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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

March 25, 2019
8:00 a.m.

FDA White Oak Campus
Building #31, Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

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M E E T I N G

(8:00 a.m.)

DR. LEWIS: Good morning. I would like to call this meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee to order.

I'm Dr. Frank Lewis, the Chair of the Panel. I'm a trauma surgeon by clinical specialty and recently retired from 15 years as Executive Director of the American Board of Surgery.

I note, for the record, that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have all received training in FDA device law and regulations.

For today's agenda, the Panel will discuss the benefits and risks of breast implants indicated for breast augmentation and reconstruction concerning the following topics: breast implant-associated anaplastic large cell lymphoma, systemic symptoms reported to patients receiving breast implants, and the use of registries for breast implant surveillance.

Tomorrow we will deal with the additional subjects of MRI screening for silent rupture of silicone gel-filled breast implants, the use of surgical mesh in breast procedures such as reconstruction and mastopexy, and the use of real-world data and patient perspectives in regulatory decision making, as well as best practices for informed consent questions between patients and clinicians.

Before we begin, I want to ask our Panel members and the FDA staff seated here at the front table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And we'll begin to my right and go around the table beginning with Dr. Chevray.

DR. CHEVRAY: Good morning, my name is Pierre Chevray. I'm a plastic surgeon who practices in the Houston Methodist Hospital system in Houston, Texas. I do mostly breast reconstruction surgery, and I'm an Associate Professor of Plastic Surgery at the Weill Cornell

College of Medicine in New York.

DR. GALLAGHER: Colleen Gallagher, and clinical ethics or bioethics is my specialty, and I'm the Executive Director of Clinical Ethics for MD Anderson Cancer Center and a professor in the Department of Critical Care.

DR. ROGERS: I'm Rebecca Rogers. I'm at the University of Texas, Austin. I'm a gynecologist.

DR. BALLMAN: I'm Karla Ballman. I'm the Division Chief of Biostatistics and Epidemiology at Weill Cornell Medicine, and my expertise is in biostatistics and epidemiology.

DR. SANDLER: I'm Howard Sandler. I'm a radiation oncologist, and I'm the Chair of the Department of Radiation Oncology at Cedars-Sinai Medical Center in Los Angeles.

DR. LI: Good morning, my name is Steve Li. My area of expertise is biomedical materials and bioengineering with particular emphasis on testing in the clinical performance related to materials and design.

MS. PAWELSKI: My name is Lynn Pawelski. I'm the Industry Representative on the Panel. I'm the vice president of regulatory affairs at Baxter Healthcare.

MS. BRUMMERT: Rachel Brummert. I'm President of Patient Safety Impact in Charlotte, North Carolina, and I'm the Consumer Representative.

DR. PORTIS: Natalie Compagni Portis, and I'm the Patient Representative today.

DR. ASHAR: Binita Ashar. I'm a general surgeon, and I'm the Director of the Division of Surgical Devices at FDA's Center for Devices and Radiological Health.

DR. ANDERSON: I'm Ben Anderson. I'm a Professor of Surgery and Global Health Medicine at the University of Washington. I'm a breast cancer surgeon in Seattle.

DR. JAFFE: I'm Elaine Jaffe. I am chief of hemopathology at the National Cancer Institute and an expert in lymphoma, including breast implant-associated lymphoma.

DR. WHITE: I'm Jeffrey White. I'm a medical oncologist. I'm the Director of the Office of Cancer Complementary and Alternative Medicine at the National Cancer Institute.

DR. LIPPMAN: I'm Marc Lippman. I'm Professor of Oncology and Medicine at Georgetown University. I'm a medical oncologist, and all of my career has been breast cancer research.

DR. McGRATH: I'm Mary McGrath. I'm a practicing plastic surgeon, and I work at the University of California, San Francisco, where I am a Professor of Surgery.

MS. ENGEBRETSON: My name is Rhonda Engebretson. I am a registered mammography technologist at the Avera Breast Center in Sioux Falls, South Dakota.

DR. BURKE: I'm Karen Burke, and I'm a dermatologist in New York City at Mount Sinai Icahn School of Medicine.

DR. LEITCH: I'm Marilyn Leitch, a surgical oncologist at UT Southwestern in Dallas where I'm a Professor of Surgery and section chief for breast and soft tissue surgical oncology. I deal daily with breast cancer patients and patients with benign breast disease.

CDR GARCIA: Patricio Garcia. I'm the Designated Federal Officer for this meeting. Thank you.

DR. LEWIS: Before we begin, I would like to -- I mean, excuse me, for topics being discussed today at the meeting, we understand there are a variety of opinions often strongly held, and our goal is to allow for a free and open discussion of all of the issues surrounding breast implants and allow the public to comment on that. We hope individuals can express their views freely without interruption. Individuals may speak into the record only if recognized by the Chairman. And I would like to note that the FDA has specifically scheduled four sessions, 1 hour each, for public input at this meeting. Those sessions will be held before lunch today and at the end of the day, and again, before lunch tomorrow and at the end of the day tomorrow. There will be four sessions 1 hour long. Twenty

members are scheduled to speak at each of those sessions, and so it's essential that we hold that to a 3-minute presentation. We realize that's quite tight, but for those of you who will be speaking, we ask that you edit your comments ahead of time in order to stay within the 3-minute limit. It's essential to do that in order to be fair to everyone and allow everyone who is scheduled to have an opportunity to present their own comments, and so we do have to enforce the 3-minute schedule very tightly in each of those four sessions.

Members of the audience, if you've not already done so, please sign the attendance sheets that are located on the registration table directly outside of this meeting room.

We now will ask Commander Patricio Garcia, the Designated Federal Officer for the General and Plastic Surgery Devices Panel, to make some introductory remarks.

CDR GARCIA: Thank you, Dr. Lewis, and good morning, everyone. I will now read the FDA Conflict of Interest Disclosure Statement.

The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a

particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purpose of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the benefits and risks of breast implants indicated for breast augmentation and reconstruction addressing the following topics:

- Topic 1: Breast implants associated with anaplastic large cell lymphoma.
- Topic 2: Systemic symptoms reported in patients receiving breast implants.
- Topic 3: The use of registries for breast implant surveillance.

On March 26, tomorrow, the Panel will discuss the remaining following topics:

- Topic 4: MRI screening for silent rupture of silicone gel-filled breast implants.
- Topic 5: The use of surgical mesh in breast procedures such as breast reconstruction and mastopexy.
- Topic 6: The use of real-world data and patient perspective in regulatory decision making. And
- Topic 7: Best practices for informed consent discussions between patients and clinicians.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Lynn Pawelski is serving as the Industry Representative acting on behalf of all related industry. She is employee by Baxter Healthcare, Incorporated.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships they might have with any firms at issue.

A copy of this statement will be available for review at the registration table during the meeting and will be included as part of the official transcript. Thank you.

For the duration of the General and Plastic Surgery Devices Panel meeting on March 25, Dr. Marc Lippman has been appointed to serve as a Temporary Non-Voting member and Dr. Natalie Compagni Portis has been appointed to serve as Temporary Non-Voting Patient Representative. For the record, Dr. Lippman serves as a consultant and Dr. Compagni Portis serves as a patient representative to the Oncology Drug Advisory Committee at the Center for Drug Evaluation and Research. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

The appointments were authorized by Russell Fortney, Director, Advisory Committee Oversight and Management Staff, on March 18th, 2019.

Before I turn the meeting back to Dr. Lewis, our Chair, I would like to make a few general announcements.

General transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting and handouts for today's

presentation are available at the registration table outside the meeting room.

The FDA press contact for today's meeting is Stephanie Caccomo. Please stand up. Thank you.

All written comments received were provided to the Panel and to the FDA review team for their review prior to today's meeting. There is an active docket where members of the public can post written comments. A link can be found on the FDA website and at the registration table.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. Artair Mallett at the registration table.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you.

Dr. Lewis.

DR. LEWIS: Thank you, Commander Garcia. We'll begin today's meeting with introductory remarks from the FDA by Dr. Binita Ashar.

DR. ASHAR: Good morning, and welcome to the U.S. Food and Drug Administration. My name is Binita Ashar. I'm a general surgeon, and I'm also the Director of the Division of Surgical Devices in FDA's Center for Devices and Radiological Health. Our division is responsible for the review and regulation of breast implants.

Before I do anything else, I'd like to acknowledge and thank the individuals on the

FDA's breast implant team who have put in a tremendous amount of work preparing for this Advisory Committee meeting.

The agenda for this meeting and the Executive Summary is in your panel pack and is also available online with copies at the desk outside. Supplementing the Executive Summary, we have invited external speakers to provide their expertise on specific topics. There are some things regarding the agenda that I would like to mention to you this morning.

First, this meeting occurs against a backdrop of several notable actions taken by international regulators as they continue to consider the benefits and risks of breast implants. Here in the U.S. we recently sent warning letters to two breast implant manufacturers because of their failure to fulfill their breast implant post-approval study requirements. To provide the perspective from international regulators, we have on our agenda representatives from both the EU and Canada who will be speaking this morning.

Over the past couple of years leading up to this meeting, FDA has been meeting with patient groups to hear their concerns regarding breast implant regulation and the communication around breast implant complications and risk. We are asking the Panel to keep at the forefront the things patients contemplating breast implants should know.

In addition to medical device adverse event reports in patient registries, FDA reviews the safety of breast implants through each manufacturer's required post-approval studies. While we know that the industry sponsored post-approval studies have issues related to post-approval study compliance, we are working with the manufacturers to analyze the available data. In preparation for FDA's Panel meeting, FDA asked each manufacturer to provide its long-term data regarding a constellation of breast implant illness symptoms. FDA conducted this exercise because while there is not sufficient evidence to show an association between breast implants and connective tissue disease diagnoses, there are

numerous breast implant patients convening on social media to discuss a wide variety of symptoms that they are experiencing. We look forward to discussing information from breast implant manufacturers regarding symptoms being referred to by patients as breast implant illness.

In 2011 FDA reported the occurrence of lymphoma diagnosed in proximity to the implant in some patients with breast implants. The finding was subsequently recognized by the World Health Organization as breast implant-associated anaplastic large cell lymphoma, or BIA-ALCL. Since 2011 we have provided regular updates on medical device reports or MDR reports of BIA-ALCL and have worked with the Plastic Surgery Foundation to develop and collect detailed information on patients diagnosed with BIA-ALCL through the PROFILE registry.

However, there is still a lot of information about these patients that is missing. In a significant number of cases, there's no information regarding the implant surface texture at the time of BIA-ALCL diagnosis. Regarding patient history of prior breast implants, there is even less information. The percentage of patients with textured breast implants who develop BIA-ALCL versus the percentage of patients with smooth implants who develop BIA-ALCL is unknown. This is because the total numbers of patients who have smooth implants versus textured implants is unclear.

So we don't know, there may be many more patients with textured implants versus smooth implants, which could explain why we have seen more reports of BIA-ALCL in patients with textured implants compared to smooth implants. Due to this missing information, we think it's important that all breast implant patients, whether we are talking about a smooth implant or a textured implant, that all breast implant patients be aware of the risk of BIA-ALCL, albeit low.

Given these gaps in data, we will be asking the Panel to consider what further steps

may be taken to understand and communicate breast implant-associated ALCL risk.

We commend efforts to understand the benefits and risks of breast implants and recognize the need for better postmarket evidence generation, including active surveillance capabilities. This is why FDA has been working with multiple stakeholders to facilitate the development of the National Breast Implant Registry and the PROFILE registries. We seek your recommendations on how to assure that however the information is collected, whether the topic is BIA-ALCL, breast implant illness, new surgical techniques, concomitant use of surgical mesh, that the information is transparent, timely, and useful for both clinical and regulatory decision making.

While we are focusing on topics related to breast implant safety, we are, at the same time, working to keep pace with changes in medical practice. For this reason we have two topics for discussion involving the implantation of surgical mesh for breast procedures. While FDA has not granted marketing authorization for any mesh device for breast procedures, we are looking at this Committee for advice on the level of clinical evidence needed to assess benefit versus risk for the use of implantable surgical mesh for specific procedures.

When the moratorium for breast implants was lifted in 2006, this Committee recommended MRI screening for silent silicone gel-filled breast implant rupture. There is long-term data regarding MRI screening that we will be presenting to you to obtain your recommendations regarding MRI screening for silent breast implant rupture.

Many people, including those undergoing reconstruction following breast cancer, choose breast implants every year. As a public health agency, we play an important role in ensuring that patients seeking breast augmentation and breast reconstruction have accurate information regarding the benefits and risks of breast implants to make informed decisions on whether implants are right for them.

The last topic on the agenda involves a discussion regarding what we can all do to ensure that patients are well informed prior to obtaining breast implants and how they may stay informed on the latest information regarding their safety.

We appreciate everyone's interest and support in getting us to this point and look forward to thoughtful discussions over these next 2 days.

I'd like to now introduce my colleague from FDA's Office of Women's Health, Dr. Kaveeta Vasisht.

Thank you.

DR. VASISHT: Good morning. As Dr. Ashar mentioned, my name is Kaveeta Vasisht, and I recently joined the FDA's Office of Women's Health as the Acting Associate Commissioner and Deputy Director. Welcome, and thank you to everyone in the room, as well as those who are viewing remotely, for participating in this important discussion about the benefit-risk profile of breast implants.

Part of FDA's mission is to protect public health by ensuring the safety and efficacy of drugs, biological products, and medical devices. The Office of Women's Health supports this mission through policy, science, education, and outreach aimed at advancing our understanding of health conditions that are unique to women or that disproportionately impact women. This is fostered through our strong external partnerships and internal relationships which ensure collaboration on considerations that are critically important to women. These collaborations have enabled us to work closely with our colleagues within the Agency to participate in listening sessions pertaining to breast implants and to support research to help bridge knowledge gaps.

As a physician, I rely on being able to share accurate information with my patients to enable them to make meaningful and well-informed choices. Robust discussion such as our meeting today are critical contributors to this dialogue. We look forward to hearing the

perspectives of our patient community, providers, academia, industry, and from other stakeholders. Thank you to the Center for Devices and Radiological Health for putting this Advisory Committee together.

Thank you.

DR. LEWIS: Thank you, Dr. Vasisht.

At this time, we'll hear a discussion by Dr. Josef Zündorf from the German Federal Institute for Drugs and Medical Devices. Dr. Zündorf, please begin.

DR. ZÜNDORF: Mr. Chairman, ladies and gentlemen, thank you for giving me the opportunity to present the contribution from the European task force on breast implant-associated ALCL.

I declare that I have no conflicts of interest.

Breast implant-associated anaplastic large cell lymphoma, BIA-ALCL, is a rare subtype of non-Hodgkin's lymphoma. In 2016, World Health Organization defined specific diagnostic criteria for this rare disease. The European task force was established to enable member states to pool data and share information on this rare disease which has proved to be a complex task, as it is a multifaceted issue.

By March 20th of March 2019 -- thank you -- 243 cases were reported to the task force, out of which 211 were confirmed cases of BIA-ALCL. Of the confirmed cases, 166 were reported to be textured implants at the time of diagnosis. These include polyurethane-coated micro-textured and macro-textured implants. The surface texture of the implants in the other reports remains unknown.

Internationally, there have been some reports of BIA-ALCL associated with smooth breast implants at the time of the diagnosis; however, the previous implant history of these reports are unknown, although a predominance of the reports of BIA-ALCL have been in patients with textured implants. To date, no controlled clinical trials that compare

homogeneous samples of patients implanted with smooth and textured implants have been carried out. The investigation into BIA-ALCL is ongoing, and as with all issues, an evidence-based approach is being taken by members of the task force.

There are several competing theories on the pathogenesis of BIA-ALCL; however, scientific proof of a causal relationship has not been established, and the cause and the mechanism for the development of BIA-ALCL is yet to be determined.

International research in this area continues worldwide. The European Commission and its Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER) advised in October 2017 that there was insufficient scientific information available to establish a methodologically robust risk assessment to investigate a possible association of breast implants with ALCL development. It was therefore seen as necessary to intensify research in the field of BIA-ALCL and to continue to devote greater attention to better understand this disease.

In this context, members of the task force participated in the workshop on BIA-ALCL organized by the Dutch National Institute of Public Health and Environment in November 2018. This concluded that given the relatively low number of BIA-ALCL cases seen per country and the variety of factors to take into account, a coordinated international and multidisciplinary approach is necessary. Future research topics include looking into the characteristics of the patient, implant, and tumor as well as biofilm formation around the implant. The participants who attended the meeting agreed to set up an international consortium with the task of preparing research proposals and planned to meet again in the second half of 2019.

When addressing questions about the continued availability of textured implants, an important consideration is that surface textures of breast implants are not all manufactured in the same way. Some literature reports that they appear to be associated with different

levels of risks. Currently, there is no international consensus on a single classification system for surface texture. A harmonized classification system would need to be established in order to collect scientific evidence on the risks and benefits of each type. The task force understands that there are various systems developed to categorize the surface type of implants and welcomes the ongoing work of the International Collaboration of Breast Registry Activities (ICOBRA) to develop an internationally agreed system. This will ensure registries are using harmonized taxonomy, which will enable future pooling of global data to aid the identification of any trends or commonality in the types of complications recorded.

Another factor to be considered is that anatomically shaped implants are commonly textured in some way. Clinically, the choice between round and anatomically shaped implants is determined by anatomic aspects of the chest wall and the patient's preferred aesthetic outcome. However, due to the BIA-ALCL discussion, the European competent authority, the ANSM in France, and some European scientific medical societies recommended preferential use of smooth implants if the outcome is acceptable.

It is understood the use of textured implants is preferred in most European countries to prevent the undesirable movement or rotation of the implants that more importantly reduce the risk of capsular contracture, which is often cited as the most common cause of revision in smooth implants. Movement or rotation is particularly desired with anatomical implants, as it could result in an unacceptable aesthetic outcome when the aim is to provide a natural looking augmentation. Additionally, there are a limited number of alternatives to the use of textured implants, and the alternatives are also associated with their own risks and contraindications.

In summary, the acceptability of the risk of BIA-ALCL associated with textured implants should be evaluated, taking into consideration the following points. First, to date,

BIA-ALCL is considered a rare disease. There have been approximately 800 confirmed and unconfirmed reports of BIA-ALCL worldwide, and this should be viewed in the context of an estimated 10 to 35 million breast implants that have been implanted as approximated in the scientific literature.

Second, the majority of known cases of BIA-ALCL in Europe involve textured breast implants. However, it has not been proven that smooth implants are not involved in the pathogenesis of BIA-ALCL.

Third, physicians should always discuss the risks with their patients preoperatively so that the patients are informed, including to be vigilant of potential symptoms indicated for this condition and able to identify them. In the vast majority of cases of BIA-ALCL, the prognosis is favorable when diagnosed and treated at an early stage. Postoperative follow-up plays an important role for early detection of the disease.

Fourth, currently there is no single classification system for surface texture used by all manufacturers.

Fifth, further research is needed to determine the mechanism of the development of BIA-ALCL and guide effective and targeted action to reduce risk.

Sixth, many individuals have reported benefits from receiving textured implants without reporting complications.

And the last point, other alternatives to the use of textured breast implants are also associated with risks and complications.

Conclusions: BIA-ALCL is a topic of significant concern, and the data is continuing to emerge. The task force's evaluation of BIA-ALCL is ongoing, and as with all issues, we take an evidence-based approach. The task force will continue to evaluate this data. There are no preventive explantation recommendations in relation to BIA-ALCL. It is imperative that the risks of having either textured or smooth surface implants are fully discussed with all

individuals before surgery so that they can make fully informed choices.

Thank you much for your attention.

DR. LEWIS: Thank you, Dr. Zündorf.

We'll now hear from Dr. Amanda Jones of Health Canada considering Ongoing Regulatory Actions and Activities.

MS. JONES: Good morning. My name is Amanda Jones. I'm here on behalf of Health Canada. I'm here with my colleague, Patrick Fandja, from the postmarket area, and I represent the premarket area. I have no conflicts to declare.

In Canada we regulate breast implants as Class IV medical devices, that's the highest-risk class, and they're subjected to the highest level of safety and effectiveness requirements.

We have three companies approved for sale in Canada: Allergan, Mentor, and Ideal. I believe all these companies are marketing in the U.S. as well.

In 2017 we did a 10-year evaluation of the breast implants to look at BIA-ALCL, and at that time we gathered distribution data from all the manufacturers, and the scope of the landscape in Canada by filler type is primarily silicone gel-filled breast implants at 73%. Twenty-six percent are saline, and about 1% are the gel/saline combination breast implants. And over that time as well, on average, there have been mainly smooth breast implants manufactured and sold in Canada, 75% smooth and 25% textured, and over that period of time we did see a decline, so it started around 50%, and then by the end of 2016, it was around 10%.

Just briefly, our premarket data assessment is very similar to the U.S. FDA's, and we followed the post-approval studies that were conducted in the U.S., and summaries of that are found on our website, summary basis decision website. Also, in 2011 we asked all the manufacturers to include ALCL in the labeling and asked for all reports to be reported to

Health Canada on an annual basis starting that year.

In 2017, as I mentioned earlier with the pie graphs, we conducted an assessment, a safety assessment, and the manufacturers provided their marketing data and their BIA-ALCL cases for that 10-year period. And at that time, we received five confirmed cases of BIA-ALCL in accordance with the WHO definition, and we reviewed the etiologic theories and risk factors; however, there was no causal link established between BIA-ALCL and breast implants. We consulted with plastic surgeon societies as well, and the recommendations were to issue a risk communication on signs and symptoms, testing steps to recognize and diagnose BIA-ALCL, as well as treatment options, and to strengthen the product labeling on the risks associated with BIA-ALCL. We also added conditions to the saline-filled breast implants which were continuously marketed in Canada since the '70s.

In terms of the topics being discussed today, I'll just go over some of the actions that we've taken or are taking currently in Canada. Starting with BIA-ALCL, we're doing an update currently to the 2017 assessment, and this will cover the safety and effectiveness profile of breast implants according to the risks for BIA-ALCL. And introduced for this have been receipt of new Canadian cases, which I'll show on the next slide. International developments, for example, recently ANSM, also the meeting in the Netherlands in November, and also newly available scientific and clinical data. And we are continuing consultations as well with the Canadian plastic surgery associations on the benefit-risk profile, particularly of textured implants in the context of BIA-ALCL.

So, to date, we have received 28 confirmed cases of BIA-ALCL. We also have 28 suspected cases. And the surface type primarily reported to date is, again, textured. No smooth implants reported in Canada with BIA-ALCL. And we have a couple non-specified as well. Filler type is primarily silicone gel-filled, three with previous saline, one with saline only. And some noticeable outcomes: We've had one case of metastasis, no deaths, and

the rest where we have the results reported have survived and are doing well.

In terms of toxicity and systemic effects, the potential for the silicone gels to induce toxic effects, in particular, was discussed in great length before the licensing of silicone gel-filled breast implants. In 2006 it was a topic of panel meetings in Canada and the U.S., and the findings of these panels and the literature and data reviewed was that silicone gel-filled breast implants and silicone implants are safe and effective, and we included labeling and patient information which was included to inform patients of potential complications.

While we have been reviewing the literature on a weekly basis since that time, we haven't done a systematic review of the literature, which we're doing right now. So, we are working on a safety review of the peer-reviewed scientific data in incidents concerning breast implant-reported systemic symptoms, as well as undergoing discussions on informed consent and communications to patients.

In Canada we have a slightly different landscape than the U.S. We have a public healthcare system, so we've taken some considerations with our public healthcare system in terms of MRI imaging. It's different in terms of what we recommend in our labeling. Since 2005, when we had an expert advisory panel, they had described this step process to determining implant integrity, which included patients taking any note of any changes in their breasts through self-exam; going to see their doctor; ordering tests, for example, an ultrasound and/or a mammogram, MRI if the results are inconclusive or negative; and going back to their surgeon and discussing the results as to whether or not they should explant.

In terms of registries, we've had several previous attempts to establish a national breast implant registry federally in Canada that have been unsuccessful. In 2006 when the gel-filled implants were licensed, Health Canada did request inclusion of an implant registration card in the packaging information for all patients receiving silicone gel-filled breast implants. However, Health Canada is again currently exploring the feasibility of a

national breast implant registry with Canadian stakeholders and under the principles of the ICOBRA, International Collaboration of Breast Implant Registry Activities.

In terms of next steps, we believe that promotion of education among patients as well as physicians in the healthcare community is key to diagnosing, treating, and tracking cases of BIA-ALCL, and we believe we really need to reach out to general practitioners, oncologists, radiologists, pathologists, and other subspecialties who will be following women with breast implants, and we're also exploring consultations with external experts at this time.

Thank you.

DR. LEWIS: Thank you very much, Dr. Jones.

We'll next hear a presentation, a clinical overview of breast augmentation and reconstruction, from Dr. Steven Nagel of the Center for Devices and Radiological Health.

DR. NAGEL: Good morning and welcome. I am Steven Nagel, Medical Officer in the Division of Surgical Devices at the FDA Center for Devices and Radiological Health. I am also a surgical oncologist specializing in breast cancer. I will be providing an overview of the meeting scope and highlights of topics from the clinical perspective.

As a surgical oncologist, I typically see patients considering mastectomy reconstruction options. When patients are candidates for breast implants, their decision may be a difficult personal challenge, and thus, their questions are based on concerns for outcome. And so to provide a view from the patient's perspective, let me take you for the next few minutes into the breast clinic to listen to the patients' concerns. These are the questions I hear as a provider guiding patients through decision making.

Breast augmentation is performed to increase the size of the breast and enhance the shape. With over 300,000 cases per year, it is the most common cosmetic surgery performed in the U.S. The implant fill can be silicone gel or saline. All approved implants in

the U.S. have a silicone shell. The shell can be textured or smooth.

While the precise market share for the different implant types in the U.S. is not known, the Panel will be asked to discuss whether the benefit-risk profile for textured and smooth implants are different for specific indications.

Breast reconstruction is performed after surgical removal of the breast or for congenital or traumatic deformity. The implant can be placed above or beneath the pectoralis muscle. The implant base reconstruction is sometimes performed with a temporary tissue expander or placed immediately, so-called direct to implant. The procedure is performed with or without surgical mesh.

While surgical mesh has not been cleared for breast reconstruction or mastopexy, the Panel will be asked to discuss benefits and risks of breast surgical mesh for specific indications, to recommend clinical trial designs, and the level of clinical evidence that should be required for a marketing application that would be acceptable to characterize these indications.

Patients have indicated they are not informed that breast implants will likely require reoperation. Breast implants are not lifetime devices. The longer a woman has breast implants, the more likely she is to experience local complications or adverse outcomes.

The Panel will be asked to discuss what additional steps could be taken to ensure that patients are better informed about the risks of breast implants.

Breast implant rupture is one of the most commonly reported events related to breast implants. For silicone implants, rupture may be symptomatic or silent, intracapsular or extracapsular.

A review of the core studies will be presented, and the Panel will be asked to discuss MRI screening recommendations for breast implant rupture.

Breast implant-associated anaplastic large cell lymphoma, also known as BIA-ALCL,

has been reported to occur years after implant placement. The real incidence is unknown; however, it has been reported to occur between 1 in 3,0000 and 1 in 30,000 patients with breast implants. Current information indicates there are more reports of BIA-ALCL involving textured breast implants than smooth breast implants; however, in 30% of the MDR reports, there is no information regarding implant surface texture at the time of BIA-ALCL diagnosis. Regarding history, there is even less information available.

As the denominator for the number of textured and smooth implants is unknown and both the patient history and the implant history is often unknown, it is undetermined if there are more patients with textured implants versus smooth implants. Due to this missing information, the Agency believes that it is important to inform all patients who are contemplating breast implants or who have breast implants of the risks of BIA-ALCL.

The Panel will be asked to make recommendations regarding next steps for the characterization, incidence, and risk factors of BIA-ALCL.

A range of symptoms that some women have attributed to breast implants have included complaints such as memory loss, brain fog, fatigue, joint pain, and rash. MDR analysis data will be presented, and the Panel will be asked to discuss methods for assessing and addressing breast implant illness symptoms.

Determination of safety and effectiveness involves assessment of benefit-risk. At the end of the day, it is the patient who gets to decide what level of benefit-risk is acceptable, so we need to provide the patient the information she needs to make an informed decision.

The Panel will be asked to discuss the role and responsibility of all stakeholders for communicating breast implant-related benefits and risks to patients.

And with that, we thank and look forward to our Panel for providing their expertise. Now we will hear from breast implant victim advocacy about what patients who have had

breast implants think the patient contemplating breast implants should know.

Thank you.

DR. LEWIS: Thank you, Dr. Nagel.

Next, we'll hear a presentation from Ms. Jamee Cook from the Breast Implant Victim Advocacy, who will speak on what patients who have had breast implants think that patients contemplating breast implants should know.

Ms. Cook.

MS. JAMEE COOK: Good morning. My name is Jamee Cook. I traveled here today from Texas. I have no financial conflicts of interest. I'd like to thank Dr. Ashar and the Panel for inviting me to speak today on behalf of harmed patients.

I got PIP breast implants in Dallas in 1998. I remember my doctor telling me about local complications, capsular contracture, rupture, necrosis, etc. That was the extent of the warnings. I was a paramedic, and I was active. Within 3 to 4 years I developed chronic fatigue and autoimmune disease. Other symptoms were swollen lymph nodes, recurrent fever, brain fog, and more. My life was greatly affected by my illness. My doctors told me that nothing could be found to explain my health problems, that I was just a tired mom and I was getting older. I was 24, so I knew it was not my age.

In 2012 my textured saline implant ruptured. I did not have the money to replace or remove it for 3 years. During that period, I developed arm and hand numbness and recurrent migraines. Upon removal in 2015, most of my symptoms went away immediately. I still battle autoimmune disease, but my life is so much better.

Several of us founded Breast Implant Victim Advocacy to help raise awareness of illness and complications that can arise from both silicone and saline breast implants, including BIA-ALCL. We've now met with the FDA on three separate occasions. We work with many other organizations and patient support groups. My story isn't as bad as the

stories we hear every single day, and it's not going to be as bad as the ones you will hear today and tomorrow. I don't even feel sometimes like my story is important anymore because the issue is so much bigger than me, it's so much bigger than even the patients in this room. We just hope to represent the women the way that they deserve.

I stand today representing thousands of women; we have quite a few here. I'd like to ask all of the BIA-ALCL patients to just quietly stand. Ladies and gentlemen, these women supposedly represent 1% of this rare disease population. Please listen to them as they share their firsthand experience of what most of you have only read about.

Now, if I could ask all the women who have been harmed by breast implants or those who know someone harmed, to stand. Not all will speak at this meeting, but they come in solidarity today to say enough is enough. Travel was a financial burden for many of them, but being physically present was important. Many are too ill to travel. We speak for them; we are their voices. Thank you.

I was asked to try to address what we believe patients need to know prior to implantation. This is complex, but what I will emphasize is I was not warned. Most ladies we speak to were not warned about most of the risk that we will discuss. There are tens of thousands of women on social media, and many tell us that the manufacturers' pamphlets were never provided. Most women say they were not well informed. What can you do to change that?

Breast implants are not lifetime devices. The FDA states that breast implants are not meant to last forever; however, some plastic surgeons say otherwise, as you can see on this website. Many women are told breast implants may last a lifetime. They tell us that newer, more cohesive implants won't rupture because you can cut them in half and nothing will happen. We've even seen videos of doctors running over breast implants with cars to show how strong they are. But the human body is a very different environment, so true informed

consent should be clear that repeat surgeries are likely and expensive because the devices don't last forever, some just a few years.

This is a 6-year old Mentor silicone implant on the right with the scar capsule on the left. This patient had three different sets and capsular contracture twice. Her list of symptoms was very long. She explanted in 2017, and her health greatly improved.

These are 2-year old Mentor silicone implants, 2 years. How many revision surgeries would she have needed if she hadn't explanted in 2017?

Maintenance, follow-up, and complications: These data are from the Mentor PMA in March 2005. Allergan's statistics are similar. FDA approved breast implants on the basis of these very high complication rates even in the first 3 years. Are patients made aware of these rates? I don't believe so.

This is an example of capsular contraction, which can be extremely painful. These textured silicone implants were just under 3 years old. They show fluid buildup and capsular contracture; fluid was aspirated and tested. Additional testing was done at the time of explant.

The FDA points out that in most cases neither you nor your surgeon will be able to find evidence of rupture by a physical examination. Breast MRIs are recommended after the first 3 years and then every 2 years from that point on. Many patients tell us they were never told to undergo MRIs to check for rupture. MRIs can cost more than $2,000, and often insurance will not pay for an MRI to check for rupture. Many women undergo mammography to check for rupture instead, but FDA's own research shows that can cause implants to leak. Shouldn't the FDA require studies to determine if sonograms can be more a more affordable alternative to MRIs to check for silent rupture?

This patient had an ultrasound and two MRIs that could not conclude whether she had a rupture. For that reason, she did not get insurance coverage for the removal. It was

not until explant surgery that they found the rupture.

Health insurance often isn't helpful. Treatment of complications from breast implants is often not covered by health insurance, even if the woman is very sick. This includes removal. Health insurance denial can prevent monitoring or radiological screening. Many women we know in support groups simply cannot afford to remove their breast implants, and insurance will not pay. There was a very large explant assistance fund, but it was so overwhelmed this last year with desperate patients that they quickly ran out of funding. When these women seek help and there is none, they can get desperate. It feels like no one will listen and no one will help. We get emails from women asking if we have any resources to help them; we have to tell these women that they have very few options.

These are some of the statements from our women.

Chemical transparency: Breast implant materials are secret. Plastic surgeons can tell you if the implant is filled with silicone gel or saline, but they can't elaborate beyond that. We have reached out to the FDA and surgeons over the last few years to ask for an ingredient list but haven't received one.

The FDA wrote the following: "Ingredients in a device is proprietary information, and only the manufacturer can release that information to the public."

Author Gail Hamilton lists ingredients for breast implants from Dow Corning trials in her book and lists on the internet known ingredients like acetone, formaldehyde, xylene, epoxy resin, and lacquer thinner.

Authors Barbara Stanistreet and Carlos Meza describe heavy metal toxicity from platinum in their books.

Full recent ingredient lists cannot be found. Cosmetics, food, and cleaning supplies all must be labeled so consumers can make an educated decision about purchasing that product. We have medical devices, however, that do not provide that information.

Surgeons can't ensure informed consent if they cannot even tell me what the product they are using is made of.

Are certain chemicals also more likely to cause BIA-ALCL? Look at these terrible rashes and skin irritations of women in our groups. Is there any doubt that this is a bad reaction to their implants?

On March 15th the FDA Commissioner put out a statement that finally acknowledges that some women have immune and inflammatory responses to breast implants. He admits that symptoms may not develop until years later, thus the need for long-term studies. His statement also says that the FDA can recall devices that are unsafe, require black box warnings, and require postmarket studies. The patients that we represent today point out that the FDA has not upheld its duty to protect the patients. Patients and clinicians have the right to this data so that full information is readily available and so that potential prescreening and diagnostic processes can be implemented.

Symptoms of implant-related illness are not widely recognized. Breast implant illness is one of 22 terms that we have found to describe the exact same symptoms. You will hear about it today and tomorrow. It is not a medically recognized disease and therefore largely ignored by the medical community. ASIA is the only term that currently has diagnostic criteria, and you will hear more about that later in the meeting.

Not every woman with implants will develop unwanted symptoms. For those that do, however, it can be devastating physically, emotionally, financially. Some women develop symptoms immediately after augmentation or reconstruction; others take several years. I have a slide above that mentions quite a few of the most symptoms that women complain of.

Many women with breast implant illness do not realize the symptoms could be caused by their implants. They go from specialist to specialist without any real answers to

explain their concerns. They are told they are crazy or made to feel that way and advised to seek psychiatric help. We are ordinary women, we are educated, we are mothers, sisters, wives, and daughters, and we are suffering. Some are ignored and laughed at, some are suffering financial strain and marital stress, some are having difficulty raising their children. Many are angry at and feel defeated by a system that has helped them. This could be someone close to you, your family member or your coworker.

I can tell you quite honestly, I never believed this would happen to me. This isn't the life that I pictured for myself. I didn't anticipate spending countless hours educating, advocating for, and listening to women. I didn't plan on working a full-time job that doesn't pay. Neither did many of the women in this room. But we do it. We do it because we don't want another woman to suffer.

This collage is just a small representation of the thousands of women who are harmed. Please keep in mind that each of them matters. Doesn't the upcoming generation of women deserve better?

These are some of the things that women show us every day; these are examples of ruptures, and these are from women that gave us permission to share.

More examples of rashes and skin manifestations. Most of these go away when removed, when the breast implants are removed.

These are contaminated implants. The top left shows discolored saline. The second shows contaminants within the implant that look like mold. The bottom shows contamination within the interior of a silicone implant. The far right is debris floating within the saline implant; it was later found to be *Aspergillus*.

This is from my dear friend, one of my cofounders. Chandra had a fulfilling and active career that was ruined by her breast implants. The implant at time of removal was not even whole. It's torn and appears to only have a portion of it left. Chandra couldn't

make this trip, but she's been a leader to our cause.

A Netherlands study in 2014 compared women there to implant patients at Baylor College of Medicine from 30 years earlier. There was no difference in their symptoms. Despite innovation in implant manufacturing, patients were still complaining of the exact same issues. There is, however, a difference in the design of the products; the components have changed. How has this affected the percentage of women harmed by implants?

Women who are sick have not been adequately studied. What are our commonalities? Is there a genetic predisposition to disease or a family history of autoimmune disease? Are we seeing an incidence in birth defects to women who have children and/or breastfeed while they have implants? We need a comparison of women who are sick with silicone and saline implants to women who have never had an implantable device.

We are currently working on a patient-driven registry to address just these issues, and the National Center for Health Research has started a similar project. We need researchers to study the issues that we think are important, not just the questions that the commissions want to address.

Social media awareness: There are over 170 groups and communities devoted to breast implant problems just on Facebook and multiple websites devoted to the same awareness. The largest Facebook group now has over 70,000 members, and it's growing exponentially every day. Our BIA-ALCL patient group is also growing significantly with women who are desperately seeking answers. We have a clinician-patient group devoted to bridging the gap between patients diagnosed with BIA-ALCL and doctors. These are women coming together globally with the same concerns and same symptoms. As told by Dr. Edward Melmed, these women didn't just meet in a coffee shop and make this up.

The feeling of finding a community where someone understands how you are feeling

is indescribable. You've found a piece to your puzzle, and you want to shout it from the rooftops. We are a family, we are a support system, we lift each other, we listen when no one else will. It's a worldwide advocacy effort. More needs to be done to ensure patient safety is not being overlooked because of profit. We need the FDA to do more.

Preemption: Harmed patients cannot hold manufacturers accountable. Because of a Supreme Court decision, patients who are harmed by Class III devices, such as breast implants, can't hold the manufacturers legally accountable. Women who have become victims of breast implants have little to no recourse against dangerous devices because the Supreme Court stated that if the FDA says a PMA is safe, it is safe. Manufacturers have been given nearly absolute immunity.

I'm here to point out very clearly today that this is not a litigation-driven movement. We can't seek our day in court. There is no monetary gain for myself or for these women. In fact, most of us end up with financial instability because of our situation: medical debt, loss of income, disability with no financial recourse to compensate us for medical expenses, lost wages, or anything else. Women who developed ALCL are offered $7,500 from the implant manufacturer, but that doesn't make up for the thousands and thousands of dollars in medical bills to treat a potentially lethal cancer. The women that are coming forward are sick. They're desperate to return to a healthy state of living. They are not here because of litigation compensation.

Flaws in mandated studies: The FDA has required post-approval studies for breast implants as part of their PMA requirements. These studies have been flawed and incomplete and should not be considered reliable. Moreover, the failure of the breast implant manufacturers to complete the PMA-required studies provides the FDA the ability to rescind the PMA and basically take away their right to market and sell the implants.

Women who were supposed to be a part of these studies were not followed up with

or were completely dropped. Some of these women had symptoms that would have been caught in data collection had the studies followed through for the complete 10 years. Some of these women developed lymphoma that would have been documented. We've heard from women who were told that their surgeon was no longer a study participant or told by the manufacturer that the study would not be continued. We've also heard from women who were completely dropped after reporting symptoms. What other data are we missing because these mandated studies were not finished?

Here are a couple of statements by women we've heard from. "I was enrolled in a 10-year study in September 2009. November 2015, 6 years into the study, I received notification that changes were being made. At this point, all follow-up appointments and questionnaires were ceased."

"Ten-year study, but they blew me off after third year. Year 2 I reported a little bit of fatigue, skin issues, and Year 3 the office no longer had a staff member assigned to the study. And Year 4, they did not return my calls."

Some mandated studies have been terminated. These studies were to look at rare events like lymphoma, cervical cancer, etc. The CDRH sent letters to the manufacturers in 2013 warning of possible revocation of their PMA if studies were not completed. It happened again this month. FDA officials told us in a previous meeting that they had the power to revoke a PMA but have never done so. If the FDA does not hold the manufacturer accountable and the legal system does not either, who will?

To expand more, we need to look at what is being said by the manufacturers. There is a possibility of risks yet unknown, which in the future could be determined to be associated with breast implants. The study size needed to conclusively rule out a risk of connective tissue disease among women with silicone gel breast implants need to be very large. It doesn't say it's been ruled out.

Literature reports have also been made associating silicone breast implants with various rheumatological signs and symptoms, such as fatigue, exhaustion, joint pain and swelling, muscle pain and cramping, tingling, numbness, weakness, and skin rashes. Studies on the effects of children and breastfeeding has not been done.

From the Ideal pamphlet: "The long-term safety and effectiveness of breast implants have not been studied. The Ideal implant has not been studied for use in breast reconstruction." But do our patients fully understand that these statements are being made?

This is my family. I gave birth to all of my children while I had breast implants. I breastfed the first two. My oldest two had birth defects and chronic health conditions. There is a level of guilt that we face as patients, wondering did my implants play a role in my children's health? The fact is we don't know, but we need to. Would I have made the same choice knowing what I know now? Absolutely not. I own my decision; I take responsibility for my choice. My choice should have been made, though, with more information. My doctor should have discussed the unknowns in depth.

The studies have not been long or large enough to tell us how often a woman gets sick from breast implants, so why are patients being treated as if their conditions and concerns are absurd? Why are women being sent to psychiatrists instead of addressing a potential issue that has yet to be recognized by the medical community? The FDA needs to be more open minded about what is known and unknown about the risks of implants and to encourage physicians to do the same. Only then will patients be informed of the risks of breast implants.

This letter from Mentor to a patient in our community shows how the manufacturer is basically ignoring any accountability. It says, in part, "Breast implants should not be considered lifetime implants due to the inherent nature of silicone, implant procedures, and

potential individual physiological reactions." It says this should be a decision between a physician and a patient. "In no event shall Mentor be liable to you or anyone else for any decision made or action taken by you in reliance of such information."

Is informed consent thorough enough? We asked surgeons to step up and do what's right; first do no harm. Help us to hold these manufacturers accountable and demand that they develop a product that is scientifically proven to be safer in long-term trials.

Adverse event data is misleading. Manufacturers, physicians, and patients can report adverse symptoms to the FDA. We encourage our women to report directly.

Recent scrutiny of safety has brought about concerns over data. From 2002 to 2017 manufacturers were provided exemptions to reporting the medical device report, MDR. These manufacturers, instead, submitted using the alternative summary report. ASRs are typically submitted on a quarterly basis and can contain dozens to thousands of adverse events in one report. These reports are not transparent to the public.

In early 2017 the FDA changed its policy. By July of 2017 the reports that had been previously submitted in ASR began arriving to the FDA in MDR. This allowed the public to have access to the thousands of reports that had previously been unavailable. So from January 2017 to October of 2018 there were at least 17,000 individual MDRs submitted to the FDA, according to Device Events.

Prior to this, patients and providers who sought to identify safety data would not have been able to see the true number of adverse events. We keep hearing that our problems went away after the '90s. They never went away. The data wasn't visible to the patients or the doctors. It's deceptive; it's not fair.

Risk of cancer: Over the next couple of days you will have the chance to hear 3-minute speeches from 9 to 10 North American patient advocates. I encourage you to pay attention to each of their unique stories and messages about their journeys of getting

diagnosed with BIA-ALCL. We strongly believe that patient real-life experience is paramount to the education and understanding of this emerging disease. That is why it is important to consider a patient representative on your breast implant advisory team.

This is BIA-ALCL, breast implant-associated anaplastic large cell lymphoma. The upper left is the typical presentation of swelling. The upper right is an example of a scar capsule mass. The lower right is the aspirated fluid from a breast seroma, the most common presentation. The bottom left is Terri, who you will hear from later. You will hear more about this disease from the women themselves, but I want to mention that we started a patient support group in early 2016. By July we had 10; now we have over 160 diagnosed women in the group. These ladies have a clearly defined disease; most of us don't. The thing is we all face harm from the same devices. Whether we augment or reconstruct, whether it's implant-related illness or cancer, we wouldn't be here today if it weren't for breast implants.

It's our understanding that one of the most paramount obligations you have as an agency is to make sure that the risks of a medical device do not outweigh the benefits. I'm going to highlight some reasons why the number of cases of BIA-ALCL is likely grossly underestimated and why textured implants and expanders should be removed from the U.S. market.

A high majority of women who have implants are not aware of BIA-ALCL. Most symptoms, pain, change in shape are thought to be part of initial complications. The longstanding message is that breast implants are the most studied device on the market, so there is presumption that they are safe. Mammograms cannot consistently detect masses within the scar capsule. Often labs and radiologists miss the diagnosis because it is misunderstood and considered rare and errors are being made. BIA-ALCL cannot be seen during surgery with the exception of the mass. Often labs and radiologists miss the

diagnosis because it is misunderstood. I already read that, I'm sorry. Please take the time to fully understand the obstacles to a BIA-ALCL diagnosis, and do not buy in to the dangerous narrative that BIA-ALCL is an extremely rare and easily curable disease without giving such statements the full and robust scrutiny that all women with implants deserve.

We do want to thank the FDA for your alert to healthcare providers as a result of our request from our last call to action from our meeting with you in September of 2018. It has helped to increase patient awareness.

Breast implant-associated anaplastic large cell lymphoma is a manmade cancer that theoretically can be eradicated by the removal of textured breast implants and expanders from the market.

A joint call to action by patients includes the following:

Mandatory standardized informed consent.

Mandate that BIA-ALCL and implant related illness risk be communicated through a patient-surgeon checklist and a black box warning.

Request patient representation on a breast implant advisory team. We are asking for two representatives: one for reconstruction and one for augmentation. Patients are not being warned, and they need to play a role in decision making.

Compliance from manufacturers reporting confirmed BIA-ALCL cases and a penalty for noncompliance. We need accountability from the manufacturers.

Use your maximum authority towards physicians and institutions to notify patients with textured implants about BIA-ALCL. Although we understand that the FDA regulates medical devices and not physicians, there is a responsibility because it has been approved by your governing body; therefore, your maximum authority should drive this call to action, and patient advocates are willing to assist with this.

Mandate studies for confirmed cases of BIA-ALCL, industry funded, and make it

public. There is no current postmarket study to monitor the women diagnosed, and recurrence of this disease is being seen in our patient group.

Change the incident narrative to emerging.

Ban textured implants or request a voluntary moratorium. I don't believe we should remove all implants from the market; that's my personal opinion. Patients do need options, but we do need to be able to offer the patients the safest option available. There are smooth implants and smooth expanders. Does the benefit of texture outweigh the risk? Ask that question of any lady in this room who has BIA-ALCL or a family member who has lost a loved one, and I am sure the answer would be no.

Increase transparency in -- sorry -- in materials used in breast implants.

Maintain individual adverse event reporting and hold the manufacturers accountable for unfinished and flawed studies. If you don't hold them accountable, who will?

We again want to thank the FDA for increasing their patient engagement. We appreciate the opportunity to voice our concerns. We want to continue open dialogue and continue to offer assistance in any way possible. I hope that you face the next 2 days with open ears and hearts. Patients are being harmed. You've heard us, and it's your duty to protect us.

Thank you.

(Applause.)

DR. LEWIS: Thank you, Ms. Cook.

We'll next hear from Dr. Nilsa Loyo-Berríos from the Center for Device and Radiologic Health who will discuss the overview of the FDA-mandated post-approval studies to date.

DR. LOYO-BERRÍOS: Good morning. My name is Nilsa Loyo-Berríos. I'm an epidemiologist by training and currently serve as Deputy Director in the Division of

Epidemiology, Office of Surveillance and Biometrics. Today I'm here to provide a high-level overview of the FDA-mandated studies for the silicone gel-filled breast implants.

In 2011 the FDA convened an Advisory Committee panel to discuss the postmarket experience of the two silicone gel-filled breast implants that were approved in 2006. At the time, the FDA recognized the large, new enrollment cohort studies that were required as condition of approval would not provide sufficient evidence on the long-term performance of these devices due to very low follow-up rates. The Panel was asked to discuss study limitations and to provide recommendations on how to better monitor the performance of these devices. The Advisory Committee meeting was also an opportunity for stakeholders to provide input and their perspectives.

The Panel recommended changes to the large study data collection tools to make it easier for study participants to complete. They also discussed leveraging safety data from other studies and to use smaller cohort studies for more common endpoints. There's also a recommendation to aggregate data or combine data across manufacturers or devices that use similar technologies.

The Panel also discussed using well-publicized registries to address rare endpoints, to find ways to establish collaborations between the FDA and stakeholders, to establish a national registry to capture real-world experience and long-term performance, and there was also mention of the need to have an update on the assessment of published peer-review literature.

Following the Panel recommendations, the large new enrollment cohort studies were redesigned with smaller cohort studies for each manufacturer. These smaller studies are designed to capture performance of the 2006 approved devices as well as of the most recent silicone gel-filled devices that were approved in 2012 and 2013. Each manufacturer is also conducting a large reoperation data collection phase with the study participants that

remained in the large cohort study.

Through collaborations with professional societies, the FDA, patients, and industry, there are now two national registries collecting breast implant data. The PROFILE registry collects data on BIA-ALCL among patients with breast implants, and the National Breast Implant Registry collects baseline data for breast implant procedures and follow-up data on reoperations.

In 2015 the Tufts report on a large-scale systematic literature review was published. This systematic literature review found insufficient evidence of an association between breast implants and lymphoma, brain cancer, cervical cancer, rare connective tissue diseases, and rare neurological events. Based on this publication, the FDA concluded that using case-control studies for the five endpoints would not provide additional value, and the case-control studies were terminated.

The FDA has different postmarket surveillance tools to continue monitoring for these rare endpoints, including medical device reporting, analysis of incoming signals, and collaborations with stakeholders in the U.S. and internationally.

Since the 2011 Panel, the FDA has maintained public webpages updated throughout the years, including data on the post-approval studies and a breast implant informational webpage.

Finally, recently compliance actions were issued on the new enrollment smaller cohort studies for Mentor memory-shaped device due to low enrollment and for Sientra due to low follow-up rates.

This concludes my presentation. Now you are going to hear from each manufacturer. They will present more detailed information on the progress of their post-approval studies, and you will have the opportunity for clarifying questions after the break. Later in the day there are going to be presentations that will include data from post-

approval studies; also, in the afternoon, you will hear more information on the two registries that I mentioned in my presentation.

DR. BROWN: Good morning, members of the Panel, FDA, and the breast implant community. I'm Dr. Stephanie Manson Brown, a plastic surgeon and the Vice President of Clinical Development for devices at Allergan. At Allergan we are committed to the health of patients, understanding science, and providing transparent communication to surgeons and patients. We welcome the opportunity to discuss the important topics that we are going to discuss over the next 2 days. I will start by giving a brief background on breast implants. I will then talk to postmarket monitoring, BIA-ALCL, and breast implant illness.

Breast implants are incredibly important for the millions of women who choose to have them implanted worldwide. Allergan breast implants are supported by significant clinical evidence, including more than 500,000 patient years from clinical studies and a large body of published literature.

Surgeons have two implant surface options to meet the individual patient needs. Smooth implants or round only, they compose around 90% of the breast implants used in the U.S. today. Textured implants are both anatomical and round and are used in about 10% of surgeries in the U.S. Outside the U.S., these rates are reversed.

The key benefits of breast implants include psychosocial improvement, such as quality of life and sexual well-being. They provide restoration of physical form for congenital abnormalities as well as for patients who suffer from loss of volume due to aging or pregnancy. They also provide an important option as part of breast cancer care, such as post-mastectomy.

As with all medical devices, patients and surgeons must give careful consideration to the risks as well as the benefits of breast implants regardless of implant surface. Textured implants include Biocell, and clearly, Biocell provides other benefits. These include

anatomical shape; improved tissue adherence, which is important for tissue stabilization; and implant stabilization. And then they also reduced the capsular contraction rate. However, cases of BIA-ALCL have been reported in patients with an implant history that includes textured implants. What is important is that the prognosis is excellent, especially when identified early and treated appropriately.

While each patient and surgical situation is unique, the literature supports textured implant use for aesthetic preference, primary cancer reconstruction, compromised soft tissue, congenital abnormalities, and patients who've had previous capsular contracture. Once again, however, a thorough discussion of the benefits and risks associated with implants is critical. I will now discuss our postmarket monitoring programs.

Following the 2011 advisory panel, FDA worked with industry to provide comprehensive postmarket monitoring of adverse events. This program can be considered in three parts: postmarket surveillance, the National Breast Implant Registry, and a large post-approval study. Additional post-approval commitments include completion of continued access study through 5 years, focus group studies of patients, patient labeling, and ongoing analysis of all returned devices. Postmarket surveillance includes medical assessment of adverse event reporting and evaluation of safety trends.

The National Breast Implant Registry collects baseline data from all newly implanted patients and those requiring reoperation. It improves time to identification of events and evaluates signals across multiple registries.

Allergan currently has one ongoing post-approval study with three arms: the BIFS arm, which collects data for round implants; the 410 arm that collects data for anatomical implants; and the NBIR data arm that collects data on reoperations similar to that of the National Breast Implant Registry.

Here we see the status of the three arms of the long-term post-approval study.

There are more than 53,000 patients enrolled in the three arms. The BIFS arm is fully enrolled with 2,000 patients; the 410 arm is partially enrolled with 421 patients. Patients who are enrolled in BIFS and the 410 arm complete questionnaires annually and return to their surgeons for scheduled office visits at 1, 4, and 10 years post-implantation to collect information on rare disease, neurological and rheumatologic signs and symptoms, as well as device-specific endpoints. Compliance with the questionnaires overall is high, in a range of around 70 to 80%, showing engagement in the study arms. We are working to improve office follow-up visits for patients by increasing contact through email, phone, text message, and mail. We're also taking measures to increase investigative engagement. Our postmarket monitoring program provides important information to evaluate the benefit-risk profile of our implants. I will now talk about BIA-ALCL.

Patients with BIA-ALCL can have an excellent prognosis when identified early and treated appropriately. BIA-ALCL is an uncommon slow-growing T-cell lymphoma that typically presents around implants, but in some of these cases it can extend beyond the capsule. The median time to onset is approximately 8 years, although the range is broad. Although the etiology is not fully understood, literature reports that higher impact surface area may increase the risk of BIA-ALCL.

The leading hypothesis centers around biofilm, and there are three likely factors that contribute to this, including procedure, products, and patient. During a procedure, bacteria can be introduced in the surgical environment. The higher surface area of a textured implant may increase the risk of bacteria accumulation. This bacterial contamination and biofilm may result in long-term inflammation. And, finally, a patient's genetic predisposition may add to the inflammatory response resulting in transformation to BIA-ALCL.

Here we see the incidence of BIA-ALCL reported in textured implants from the

literature. As you can see, BIA-ALCL, while uncommon, is variable across countries. Additionally, we see a wider range of incidences reported in Australia, which may speak to clustering of cases, potential genetic or surgical technique components. Allergan's postmarket surveillance data shows a worldwide BIA-ALCL incident rate of 1 in 32,000 when Biocell textured implants were in place at the time of diagnosis. When we look at the U.S., we can see incidence rates of 1 in 16,000.

These are from our 410 continued access studies, which included only Biocell implants, shows an incident rate of one in 3,000. These rates for Biocell are higher than reported across manufacturers and may represent the effects of procedure, patient genetic predisposition, and/or environmental factors.

Evidence suggests that BIA-ALCL mitigation can be effective. To mitigate an introduction of bacteria in the surgical environment and subsequent biofilm formation on higher surface area implants, an enhanced 14-point aseptic protocol has been proposed. Off of the 14 points, enhancements include changing gloves between implant sites, soaking the implant in antiseptic solution, and the use of minimal touch technique. When these and other steps were taken, researchers reported zero cases of BIA-ALCL in 42,000 Biocell implants with a mean follow-up of 11.7 years. These data underscore the value of continued communication on the importance of aseptic technique.

In addition to mitigation strategies, evidence suggests that BIA-ALCL treatments are effective. When patients notice swelling or less commonly pain, it is important that they seek medical support early because early identification and appropriate treatment are critical for best outcomes. For the large majority of patients, implant removal with surgical capsulectomy alone is completely effective. In addition, a novel targeted treatment in advanced disease is effective with complete remission being demonstrated with brentuximab.

We at Allergan remain committed to improved awareness through educational activities for surgeons and primary care providers, working with international medical societies to increase awareness with patients and physicians, global scientific roundtables, online seminars, consensus statements, and journal supplements, and making patient materials available including a website and brochures. Secondly, Allergan realizes insurance coverage can be an issue, and we are committed to the ongoing use of internal resources to assist surgeons in obtaining coverage for patients in these circumstances. And, finally, we provide financial assistance to patients for seroma evaluation and for any treatment associated with BIA-ALCL.

Furthermore, Allergan remains committed to improve awareness through research. We absolutely want to understand the cause of disease so we can help patients. We are doing this through both independent and internal research. With independent research, we are supporting work in immunology, looking to the cause of BIA-ALCL and genetic associations. Internally, we're working on infection control through the efficacy of aseptic solutions and exploring the impact of textured surface area and bacteria colonization and developing lower surface area textured implants.

Our last topic is breast implant illness. As noted by Drs. Gottlieb and Shuren from FDA, there are patients who are concerned that the symptoms they are suffering from are related to their breast implants. There are over 80 signs and symptoms that have been reported under the term breast implant illness, such as cognitive issues, fatigue, and muscle pain. We empathize with these women and can only imagine how distressing this is for them.

While no established case definition exists and the time to onset following implantation varies by patients, it is imperative that we seek to understand breast implant illness despite the challenges with clinical evaluation. The key challenges are, firstly, we

don't currently have an established case definition. Secondly, similar symptoms can present in patients without breast implants. And, third, we lack standardized assessment tools to compare data that been collected.

However, currently we are actively monitoring a post-approval study, data to look for links between implants and symptoms. We also regularly communicate with FDA regarding postmarket surveillance and provide a medical assessment of every single reported event.

With these next steps in mind, our recommendations are for close cooperation between patient groups, industry, regulators, and experts. We want to continue work on improved symptom to disease mapping and also recommend independent epidemiological review of signs and symptoms data from large post-approval studies.

So, let me close by highlighting the following points. Breast implants are backed by significant, long-term clinical experience and comprehensive postmarket monitoring. Evidence supports that breast implants, including Biocell textured implants, provide important benefits to women who choose to have them implanted. The incidence of BIA-ALCL is low, and when identified early and treated appropriately, prognosis is excellent.

We continue to listen to patients and evaluate signs and symptoms from each patient case individually. Evidence supports that the benefits of breast implants outweigh the risks. And we are committed to working with FDA and other parties to get best outcomes for patients.

Thank you for your time.

DR. LEWIS: Thank you for your presentation.

I'll now ask for representatives of Mentor to make their presentation.

MS. DAURIA: Good morning, Mr. Chairman, members of the Advisory Committee, and the FDA. My name is Raina Dauria. I'm Vice President of Regulatory Affairs supporting

Mentor. At Mentor, patient safety is our first priority. We want to thank you for the opportunity to present our perspective on breast implant safety and risks. I'll begin with an update on the potential risk factors associated with breast implant-associated anaplastic large cell lymphoma. I'll then present our data relative to the occurrence of systemic symptoms followed by a commentary on the use of registries for the continued surveillance of breast implant. I'm joined today by additional experts who can help me answer questions as needed.

Mentor gel and saline breast implants are supported by long-term clinical data including three 10-year prospective clinical trials. They're sold in more than 80 countries and have been chosen by millions of women worldwide for over 30 years.

This slide captures the number of observed patient years for some of the key post-approval studies completed using our gel-filled breast implants. It also reflects our two prospective post-approval studies that are currently being conducted to address some of the unanswered questions related to breast implant safety.

Last week Mentor received a warning letter for the combined cohort study specifically related to the enrollment in the MemoryShape group. The MemoryShape implants are available with a textured surface only. Over the last several years, the use of textured devices in the U.S. has decreased substantially. As a result, Mentor has been challenged in enrolling this study group despite taking steps to increase enrollment. We look forward to working with FDA to address these concerns.

So, let's begin with BIA-ALCL. While highly curable if detected early, BIA-ALCL is a serious condition. It is generally accepted that women with breast implants are at an increased risk of developing this lymphoma. What is not fully understood is why. Many factors have been suggested as contributing to the development of BIA-ALCL. The true causality of this disease is likely multifactorial. Recent publications have noted differences

in the number and type of bacteria referred to as biofilm present in the capsules from patients diagnosed with BIA-ALCL. Others have suggested that particulate matter present in the breast capsule may be a contributing factor. In fact, our own research has shown that implants from different manufacturers have varying amounts of free or loosely attached silicone particles on their surfaces. More recent studies have suggested genetic predisposition, and some have pointed to surface texture as an important influencing factor, which I will discuss next.

Implant surface texture varies greatly across manufacturers. Looking at the scanning electron micrograph images of implant surfaces for various manufacturers, we see the surfaces are quite unique. Mentor imprinted shell surface, shown on top, has small peaks and valleys while others have a lattice-like pattern and still others show holes or crevices. These patterns create differences in surface area. Studies have suggested that the greater the surface area, the more bacteria may adhere to the implant surface. A greater amount of bacterial biofilm is thought to contribute to a higher level of chronic inflammation, which may lead to the development of BIA-ALCL. This is reinforced by published data which show that textured implants made by different manufacturers have different BIA-ALCL occurrence rates.

This graph shows that the cumulative proportion of patients with BIA-ALCL over time with Mentor textured implants remains low compared to other textured implants with a greater surface area. While not a randomized controlled study, this observational study analyzed all reported cases of BIA-ALCL in Australia and New Zealand between 2008 and 2018 and took into account the surface texture as well as texture sales data dating back to 1999 obtained directly from the leading breast implant manufacturers, including Mentor. These two pieces of information allowed for the risk of BIA-ALCL to be estimated per specific implant and surface type. For Mentor imprinted texture implants, the risk of

BIA-ALCL was rare, 1 case in 86,029 implants. This incidence rate was 16- to 25-fold lower than that observed with other textured implants.

Other published BIA-ALCL studies conducted in several different countries reinforce these results. The number of BIA-ALCL cases reported in patients with Mentor implants is low in comparison with the total number of cases identified. For years, Mentor has maintained either higher or roughly equal breast implant worldwide market share with the next leading manufacturer; therefore, the low number of BIA-ALCL cases cannot be accounted for by differences in sales volume. While Mentor textured implants have a low rate of BIA-ALCL, it remains a significant concern for us; however, textured implants offer important benefits for patients and do still have a place in the array of patient choices. These benefits include reduced risk of reoperation due to capsular contracture in subglandular augmentation patients and asymmetry in reconstruction patients as compared to smooth. In addition, textured implants offer the benefit of less movement and rotation within the capsule. Finally, shaped implants are an important option for physicians and patients and they're only available with a textured surface.

We would also like to take this opportunity to comment on some recently introduced breast implant classification systems that were designed to characterize surface properties. It's our position that implant-specific long-term clinical data are the best reflection of an implant's performance since benchtop classification methods are not harmonized and, more importantly, are not clinically validated.

Now I will shift topics to systemic symptoms. Some women with breast implants have reported a range of systemic symptoms. These may present differently in different patients, and while the causes of these types of symptoms can be difficult to determine in any person, we consider patient safety and reported symptoms very seriously, and we understand the need to monitor them continuously through both internal and external

sources, including our own clinical study data and safety surveillance activities.

We would like to share a few findings now, and additional data has been provided in the briefing packet. We've analyzed data from our MemoryGel and MemoryShape core studies to look at various systemic symptoms. Presented here are the percentages of new reports, over time, of fatigue, insomnia, and joint pain after implantation of the MemoryGel implant on the top row or our MemoryShape implant on the bottom row. The line graphs show no consistent increase in reports of newly developed fatigue, insomnia, or joint pain with longer exposure to the implant. However, Mentor is committed to continuing to examine the possible connection between systemic symptoms and breast implants through grants and registry support, our own internal extensive ongoing postmarket surveillance, and of course, post-approval studies.

This brings us to our next topic, the use of breast implant registries for continued surveillance of breast implant safety. Today you will hear about the National Breast Implant Registry and the PROFILE registry. Mentor believes that these registries can be used to address some of the open questions related to breast implant safety. The NBIR will allow surgeons and manufacturers to track and trend their data using its analytics capabilities. The PROFILE registry is already filling in the gaps on BIA-ALCL cases in terms of the number of cases and critical details, so the potential risk factors can be identified.

Here are some of our specific recommendations to improve the NBIR's collection of clinically meaningful data. We're suggesting that a random sampling of women participate in a sub-study that allows for the collection of additional risk factors at the time of entry into the NBIR and ongoing thereafter. Examples of additional risk factors to be monitored include family medical history and complete breast implant history.

Genetic marker testing may also be conducted as recent studies have shown that some patients may be genetically predisposed to the development of BIA-ALCL or systemic

symptoms.

Finally, capsular tissue may be analyzed for biofilm at the time of explantation. Equally important is the collection of outcome data such as the occurrence and the severity of immunological, rheumatological, and neurological symptoms. We would recommend that monitoring does not stop at implant removal, but that valuable information can be collected by the continued collection of data post-explantation.

A patient's quality of life should also be assessed using a validated tool such as the BREAST-Q.

In summary, Mentor fully supports the NBIR and considers this registry, along with the PROFILE registry, as our best means for collecting long-term clinical data that will inform us about the safety of breast implants.

As patient safety is our first priority, we support open and transparent dialogue so that women have all of the information needed to make informed choices about their breast surgery.

To close, we would like to emphasize that we see this effort as a shared responsibility. We look forward to the discussion today and partnering with surgeons, patients, and the FDA to identify additional ways that we can educate patients, their caregivers, and their physicians about the benefits and risks associated with breast implants.

Thank you very much.

DR. LEWIS: Thank you for your comments.

We'll now hear from representatives of Sientra.

MS. KUHNE: Good morning. Sientra is pleased to present today to the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee. My name is JoAnn Kuhne, and I'm Vice President of Regulatory Affairs and Quality Assurance at Sientra.

I am joined by my colleague, Rosalyn d'Incelli, Vice President of Clinical and Medical Affairs, and Dr. Jennifer Harrington, Sientra's medical director.

Patient safety is our highest priority, and although not required by FDA as a condition of PMA approval, we believe that providing our products to only board-certified plastic surgeons results in the best patient outcomes. We're the only company who supplies our implants solely to board-certified plastic surgeons.

Our core clinical study is the largest pivotal breast implant study in the U.S., and our 10-year data from completed long-term study demonstrates that our Sientra Opus implants remain safe and effective for use in breast augmentation and reconstruction.

Based on a commitment to collect long-term real-world data to advance the science of plastic surgery and optimize patient outcomes, we will continue to support the research and educational opportunities through our partnerships and collaborations with board-certified plastic surgeons, medical societies, and other medical and scientific experts. And based on our confidence in our long-term implant performance and commitment to patients and surgeons, Sientra offers the Platinum20 program, a 20-year implant warranty, the longest duration of coverage and most complete warranty in the industry.

As further committed to patients and the advancement of education and awareness, Sientra developed the Full Circle platform, a first-of-its-kind charitable program that supports breast cancer nonprofits committed to making a meaningful difference in patients' lives. In supporting these philanthropies, Sientra donates a portion of revenue from every Opus breast tissue expander sold to the Full Circle fund.

Turning to our portfolio of products, each Sientra Opus breast implant is composed of a silicone elastomer shell filled with our high-strength cohesive fifth generation gel. Sientra Opus implants are available in a range of shapes, profiles, and sizes as well as in smooth and textured shell surfaces. Sientra's unique textured shell surface is created by

our proprietary heat volatilization process.

The next section outlines Sientra's post-approval studies. Per a PMA approval order, we have six conditions of approval. These conditions include conducting long-term clinical studies, conducting a focus group study concerning our patient labeling, and participating in the development and implementation of the National Breast Implant Registry. As you can see from the slide, we have successfully completed three of the six commitments, and two are ongoing. We completed our 10-year PAC study, which is the continuation of our pivotal core study; our 5-year post-approval continued access study; and focus group study that informed our patient labeling. One post-approval study was rescinded by FDA because it would not provide any additional value given that the Tufts University systematic review showed a lack of evidence associating silicone gel-filled breast implants with several rare events. Our 10-year U.S. PAS study is currently ongoing, having just completed 3 years of follow-up. This one post-approval study is the subject of the recent warning letter FDA issued to us last week related to our follow-up compliance.

Even with Sientra's concerted and continued efforts, including patient and site compensation, accommodation and repeated contact methods and study site assistance, our follow-up compliance is lower than expected. There are industry-wide challenges regarding achieving sufficient patient follow-up in clinical studies. In Sientra's efforts to contact patients for follow-up, participants' reasons for not complying with study commitments include the challenges of everyday life, such as childcare and work responsibilities. Furthermore, the study population is generally healthy; most are not having any problems with their breast implants and therefore do not feel the need to return for study follow-up visits. We're currently examining alternate and innovative ways to address this challenge. We are committed to meeting patient retention requirements and will work with the Agency to immediately address this important issue.

Going forward, additional strategies include increased site and participant support, including increased financial incentives and frequency of contacts as well as expanded frequency of online and social media searches to locate participants. Sientra will work with study sites to evaluate innovative and more effective strategies to address these challenges.

Registries can lead to better utilization of resources and data collection across a significant population of women receiving breast implants and may address challenges experienced with traditional post-approval studies. Since its inception, Sientra has been an active participant in the development and implementation of the National Breast Implant Registry, which you will hear more about later today. We remain dedicated to the registry as a member of the steering committee and by providing funding along with other contributors to support the registry charter.

A unique aspect of the National Breast Implant Registry is its intent to serve the dual purpose of also facilitating FDA's mandatory breast implant device tracking requirement. This reduces the burden of multiple data collection efforts for surgeons and their staff and therefore functions as an incentive to the plastic surgery community to contribute their patient data to the registry.

Moving on to the long-term data we've already collected in our 10-year PAC study, Sientra's completed PAC study is the largest pivotal study conducted in the U.S., including nearly 1,800 patients and over 3,500 devices. Devices implanted included an almost even split of surface device characteristics. Our 10-year PAC study data for the primary augmentation cohort included over 1,100 patients.

Regarding key complications, capsular contracture was reported at approximately 13%, rupture at 8.5% in the almost 400-patient MRI cohort, and reoperation at 24%. For the revision augmentation cohort, rates at the same key local complications were similar to the primary augmentation cohort. Of note is that the most common reasons for

reoperation was breast implant style or size change.

In the primary reconstruction cohort, capsular contracture hovered around 16%. Rupture was reported at 16.5% and reoperation at a rate of about 48%. No ruptures occurred in the revision reconstruction cohort, and the rate for capsular contracture and reoperation are similar to the primary reconstruction cohort.

In the PAC study, over 40 individual connective tissue disease-related signs and symptoms were collected and analyzed using 13 multi-symptom categories, including the categories of joint, fatigue, and fibromyalgia. For the pooled augmentation and revision augmentation cohorts, compared to before having implants, there were no significant increases in any of the 13 CTD categories. However, there were significant decreases found for three of the categories: neurological, endocrine/exocrine, and vascular. No significant increases or decreases were found across any of the 13 CTD categories in the reconstruction and revision reconstruction cohorts.

Sientra's 5-year PACAS study arm was completed in 2013 and included augmentation and revision augmentation cohorts. The PACAS study included over 2,500 patients and over 5,000 implants. Similar to the PAC study, there was a fairly even percentage of smooth and textured devices included in the study. The augmentation cohort included over 2,000 patients and revealed relatively low rates of capsular contracture, rupture, and reoperation through 5 years. No ruptures occurred in the PACAS revision augmentation cohort of almost 500 patients. Capsular contraction occurred at around 13%, and reoperation hovered around 31%.

Thank you for your attention. I'll now turn the presentation over to my colleague, Rosalyn d'Incelli, to discuss our new enrollment post-approval study and the topic of BIA-ALCL.

MS. d'INCELLI: Thank you, JoAnn.

Good morning. We commenced our post-approval study upon FDA PMA approval. I don't think my slides are up. Wait for slides.

(Pause.)

MS. d'INCELLI: All right. The 10-year U.S. post-approval clinical study was designed to study the real-world long-term clinical performance of Sientra's implants under general conditions of use. Over 5,000 implant participants were enrolled and 300 plastic surgery controls at 138 United States clinical study sites. The study is currently in its fourth year of follow-up, and as discussed, continued and concerted efforts have been employed to increase that follow-up.

Looking at the key complications thus far, for primary augmentation there's a 1.6% capsular contracture rate; 3.9% rupture rate which includes unconfirmed and confirmed ruptures; and a 6% reoperation rate. Within the revision augmentation cohort, there is a 4.1% capsular contracture rate, no ruptures, and 11.8% re-operate. For both reconstruction cohorts, capsular contracture and re-operates are similar, and there were no ruptures in either of the cohorts.

On the topic of BII, we have studied the signs and symptoms by collecting over 30 individual symptoms such as fatigue, joint pain from participants, both implanted patients and control participants at 2 years. These symptoms were analyzed in two categories: rheumatologic and neurologic. The incidence rates importantly found that there was no statistically significant difference between the control and the implant group.

Another very important topic of this Panel is breast implant-associated ALCL. Sientra takes BIA-ALCL very seriously and continues to support all of the medical research, education, awareness, and initiatives to better understand this condition. This important topic will be discussed in more detail later today by both Karen Nast from FDA and Dr. Mark Clemens from MD Anderson.

In regards to Sientra's reported cases in patients with BIA-ALCL, we have three primary cases. They were diagnosed between 6 to 10 years postoperative. And we have two non-primary cases. These patients both have a similar history. Both were revision reconstruction patients with previous implants from another manufacturer for 9 and 13 years. Both patients were explanted due to seroma and then re-implanted with Sientra devices with subsequent seromas approximately 1 year after placement. For our five patients that have been diagnosed, the implants and capsules were removed and there was no further treatment. These patients all remain disease free, most importantly.

ALCL rates vary among implants, geographics, and many other factors as you have heard, and you will hear further. Recently, FDA reported a risk rate range of 1 in 3,000 to 1 in 30,000. A recent peer-reviewed publication from Calobrace et al. reports a Sientra rate of 1 in 200,000.

Our professional outreach is one step we take to support BIA-ALCL research and education. The joint statement you see here is one example of creating awareness and information to plastic surgeons on the known risks, symptoms, diagnosis, and treatment for BIA-ALCL.

In addition, we sponsored two recent education publication supplements on ALCL and are a contributor and member of the BIA-ALCL fund that provides financial assistance to under- and uninsured women who are diagnosed and need surgical treatment.

In addition to these joint efforts, we drive numerous education materials. Our product labeling provides information related to BIA-ALCL as well as all other surgical outcomes, considerations, benefits, and risks. Sientra's surgical best practices 14-point plan is authored by expert BIA-ALCL researchers, and this resource educates surgeons on best surgical practices to reduce bacteria-related implant complications. All of these efforts and communications were driven by Sientra in order to support research and increase

awareness to plastic surgeons and their patients.

Patient safety and product quality is Sientra's highest priority, and that's why we only provide our implants to board-certified and board-eligible plastic surgeons, the most highly trained to perform these procedures. We will continue to be guided by the science behind our products. The final results of our 10-year core study demonstrate that Sientra's implants continue to be safe and effective, and importantly, the majority of patients report high satisfaction with their breast implants and their decision to undergo breast implantation through 10 years of surgery postop.

Sientra appreciates the value that breast implant registries contribute to this growing body of knowledge. To that end, we will continue to actively support the NBIR and collaborate with experts, societies, and FDA to increase education and research. Sientra recognizes that this research is important for women and that the decision to undergo breast implant surgery is a very personal choice. Sientra is committed to safety and wants women to feel confident that they are making an informed decision based on all of the benefits and risks of Sientra's extensively researched FDA-approved breast implants.

Thank you.

DR. LEWIS: Thank you for your comments.

We'll now hear from representatives of the Ideal company.

DR. HAMAS: Good morning, everyone. Long morning so far. My name is Robert Hamas. I'm a board-certified plastic surgeon, and I've been in private practice in Dallas for 37 years. Listening to my patients over the years, I realized that there was a need for a new type of breast implant, something really quite different than had been on the market. I was listening to women talk about why there wasn't something that combined the best of both. And I thought that maybe there would be a way to develop a solution to some of the problems with the existing saline and silicone gel implants and that would require a whole

new technology. So, I think we do need a new technology implant, and that's what I set about developing shortly after the gel moratorium in '92.

The silicone gel implant is really old technology. It has a nice natural look and feel, and the cross-link silicone gel supports the shell, so it supports tissue in situations like reconstruction. But our society wants more natural things these days, organics is the word, and the gel in the implant concerns some women. Rupture replacement with a silicone gel implant typically involves a capsulectomy, a little more complex procedure, and taking out a ruptured gel implant is a mess. I think I speak for every plastic surgeon; it's certainly not something you look forward to because of the nature of the gel and how it sticks to the tissues.

Ruptures are silent, and we've talked about needing detection with an MRI scan, and this is the 10-year rupture data from the clinical trials for primary augmentation. And I think it's important to know that women are bothered by the idea of a ruptured implant. It doesn't matter to them whether it's intracapsular or extracapsular; ruptured is ruptured, and they just don't want a ruptured implant in their body. But what happens after 10 years? We see 10-year data thrown around a lot, but this is just an example; if you can follow these lines and look up in the future, the rates are really quite high.

So how have women viewed their implant choices? The saline implant, the water balloon, certainly has the safety of saline and no need for MRI scans, but there's compromises. It has an unnatural feel, and there's no support inside the implant, so it collapses when upright. The silicone gel implant, of course, has the benefits that we talked about, natural looks and feel, but the compromises are that the ruptures are silent, and you need an MRI scan to diagnose rupture.

So, I think women clearly want a third choice. They'd like the best of both, and this is what evolved after many years of work and development. And it's a saline-filled implant,

there's only saline in this but no silicone gel at all, and the layered shells provide the structure, much like cross-linked silicone gel does. So, the shells or baffle shells control the saline movement, and what this does is alter the fluid dynamics so that the implant has a feel very similar to natural breast tissue.

We did our clinical trial and started in '09. We're at the 8-year mark now, and our data is looking very good. We're very pleased that the rupture rate -- we compare to gel implants usually -- is low and the capsular contracture rate is favorable as well. So, performance-wise, the implant seems to be doing well from the trial.

So how do women view the Ideal implant? We've tried to understand quite a bit what's important to women. One of the things they really like is the ability to look in the mirror and know their breast implant is intact. There's no risk of silent rupture, no need for MRI scans, and of course, saline is natural and absorbed in case of a rupture.

We've been on the market for 3½ years. Most of you have probably not heard about it, so I'm pleased to have the opportunity to tell you about this implant. What we have found is that women who choose Ideal Implant are more health conscious. They've become well informed through online research; many have had prior implant surgery, perhaps ruptured gel implants, and want them changed.

The surgeons who choose this implant and offer it to their patients tend to be very unbiased, they make a point of that, and they want to offer their patients all three types of implants: the saline water balloon, the silicone gel implant, and the structured Ideal Implant. In this short period of time, we've fortunately not seen any cases we're aware of with ALCL or even breast implant illness.

Mastectomy is kind of an interesting situation for women. ASPS statistics show that only 5% of breast reconstructions are done with saline-filled implants, the water balloon, and as you can understand, there's no support and you don't have a very good feel,

especially with thin tissue over it. So, 95% of breast reconstructions with an implant are done with silicone gel implants, which was said earlier supports the tissue. Now, Ideal Implant also supports the tissue and it also has a natural feel but also the advantage of having only saline, which many women would like, but it's not an FDA-approved option for reconstruction because being a small company, a startup, we did not do reconstruction in our clinical trial. So, women cannot be informed about this option by us, and women effectively have no choice if they're going to use an implant for reconstruction; they're pretty much forced to have a silicone gel implant.

Now, if there was a reconstructed indication for the Ideal Implant, women would have an approved -- excuse me, alternate to silicone gel, which they may like; they might appreciate no silent ruptures, no MRIs, no capsulectomy if there's a failure, and still have a natural feel. Women could be informed, then, about this option. They could, on their own, compare the benefits and compromises of all three implant types and they could make an informed choice. Women could choose the option that they think best fits their own personal needs.

So, in the practice of medicine we have found that over the last 3½ years, about a hundred surgeons have used the Ideal Implant for breast reconstruction. Many have repeatedly used it, so that means, you know, they're happy with the results and doing more. What the surgeons tell us is they feel they're getting good outcomes, they have happy patients, and this implant is effective for breast reconstruction. Women say it fills an unmet need for an alternative to silicone gel, and who knows, it may become the preferred option for mastectomy reconstruction in the future.

How do we get to a reconstructive indication? Fortunately, there's a real-world experience pathway available where we can collect safety and efficacy data from the cases that are already done, from the medical records. These are verifiable source documents

that are subject to monitoring, which would provide accurate and reliable real-world data and real-world experience with the Ideal Implant. This data should be of sufficient quality to support FDA's regulatory decision, and after all, we're simply looking to add a reconstructive indication for an already approved implant with over 8 years of clinical trial, and we're planning to start just such a study very soon. So, this implant was developed to be a solution to some of the problems with the existing implants.

Thank you for your time.

DR. LEWIS: Thank you for your comments. We'll now take a 10-minute break and return at 10:25. At that time, we will have a 15-minute period for members of the Panel to ask clarifying questions of the four representatives of the companies which make implants, so consider your questions during the recess, and we'll start that immediately on return. Thank you.

(Off the record at 10:15 a.m.)

(On the record at 10:28 a.m.)

DR. LEWIS: Could we have representatives of the four companies please take their place in front of the podium so that we can ask questions?

(Pause.)

DR. LEWIS: Could all of the representatives please take their position over here in front of the podium so that you can speak up to the microphone directly? And, Panel members, please raise your hand if you have a question.

Yes. Dr. Portis.

DR. PORTIS: Yes. Well, I guess first I have a comment, and then I have some questions. I just want to say that the repeated assurances that ALCL is highly treatable is small comfort to women who are undergoing the physical, emotional, and financial realities of having this disease. So as a patient myself and as the Patient Representative, I really

urge you to consider that in the presentation because being told it's not a problem, we can treat it, when for many of these women they already have had a primary cancer diagnosis, so just something that I want to mention.

(Applause.)

DR. PORTIS: But I do have some questions. So, when you're talking about doing further research, I wonder what underlying risk factors and genetic predispositions you're planning to look at. Also, any intention to look at diverse populations. And my third question is, have you considered giving a complete ingredient list so patients would have that information?

DR. LEWIS: Who would like to address that?

MS. DAURIA: Raina Dauria, Mentor.

So, your first question, if you could repeat your first question.

DR. PORTIS: What underlying risk factors and genetic predispositions do you think it would be useful to look at?

MS. DAURIA: Certainly. So underlying risk factors that we would recommend include family history of potential diseases or rheumatological or neurological disease states and also a history of cancer or anything else like that.

And then you asked about diversity, and we do include diverse populations in our clinical trials, so we absolutely do that, and we think it is important to include a diverse patient population.

DR. PORTIS: Should you think that -- are you already seeing some predisposing factors? I noticed there was some mention in some of the materials that some of the companies said about things like vitamin D_3 deficiencies and other things like that.

MS. DAURIA: We have seen in published literature that there is a potential predisposition. I don't know if there's enough data to support that yet, so we do

recommend collecting all of that. I would welcome Dr. John Canady, who's from our medical affairs group, to comment more from a clinical perspective.

DR. CANADY: John Canady, Medical Director for Mentor. I'm also a plastic surgeon. Your question was around vitamin D_3 deficiencies and other preexisting types of things. For a lot of diseases, there's continually evolving insight into preexisting types of issues, and as Raina said, I think a lot of those are first discovered in studies that are published in the literature, and then it becomes a matter of trying to sort out which of those are likely to have the biggest impact or be most frequent to be included in the clinical studies. So yes, certainly, we would look at those going forward.

Anybody else want to --

DR. LEWIS: Let's move ahead to the next question, if we can. We've got a lot to cover.

DR. HAMMER: Okay. Dr. Jason Hammer, Allergan, global medical affairs. At Allergan we're conducting basically three categories of research currently. We're conducting our internal research, we're supporting external research, and we're involved in new product development. For internal research, we're evaluating the impact of the textured surface areas; we're looking at antiseptic solutions. External research is focused mostly on epidemiology, immunology, basic science and genetics, some of the contributors that have been postulated in the literature and evolve towards that leading theory of biofilm and how it interacts with the implant surface. And, finally, we are actively exploring new implant technologies.

DR. LEWIS: Thank you.

I have a question for the manufacturers who make both silicone and saline implants. If it's not beyond your proprietary information, is there any difference in the capsule of saline versus silicone implants?

MS. CARTY: Kelly Carty, Director of Regulatory Affairs for Allergan.

DR. LEWIS: Speak up a little bit.

MS. CARTY: I'd like to ask Dr. Mark Jewell to speak about that.

DR. LEWIS: The ones that enclose the shell, the shell of the implant itself.

DR. JEWELL: Mark Jewell. I'm a practicing plastic surgeon from Eugene, Oregon, associate clinical professor at Oregon Health Science University, and a consultant for Allergan. You've asked the question is there a difference between saline and silicone-filled implant shell capsules, and the answer is they're very similar. A smooth capsule with a saline device, a smooth capsule with a silicone device that is intact basically is the same. Textured response with Biocell shows tissue integration and a somewhat disordered array of collagen on both implants.

DR. LEWIS: Thank you.

Yes, Dr. Rogers.

DR. ROGERS: I was wondering if any investigations have been done regarding the impact on breast milk and chemicals, or whatever is released into breast milk, as well as the impact of implants on ability to breastfeed.

MS. DAURIA: Thank you. Raina Dauria, Mentor.

Mentor did include in our large core study, as well as our PAS study, the potential effects of breast implants on breast milk and including offspring of patients, and we did not see any evidence of any transference of materials into breast milk.

MS. d'INCELLI: Rosalyn d'Incelli from Sientra.

We do collect reproductive and lactation outcomes in our core pivotal trial as well as our post-approval study, and thus far, in the analysis, there's been no increase or association, or risks identified in those cohorts. So, we're continuing to follow that, but there's been no increased concern in that area.

DR. LEWIS: Thank you.

Dr. McGrath.

DR. McGRATH: One thing that I think will help us to understand things today is to have a better sense of how many of the implants that are currently being sold in the United States are textured versus smooth surface. I had always thought we had about a 12% use of textured implant and 88% smooth surface, but I understand from some figures now that it's probably more of like 90/10 with only 10% textured but that plastic surgeons are moving away from using the textured surface. I'd like to get a sense of what you're seeing right now with your sales figures on that, roughly, proportionally. I think that would give us some help. It's entirely different from the rest of the world, where you can flip those statistics almost completely.

MS. CARTY: Kelly Carty, Allergan.

As you saw in our presentation, we see 90% smooth and 10% textured.

MS. DAURIA: Raina Dauria, Mentor.

We also see 90% and 10%. We do know that only less than 5% of our sales are with the MemoryShape textured implant.

MS. KUHNE: JoAnn Kuhne, Sientra.

I can't speak to the sales numbers, so what I can tell you is from our device tracking numbers where we used to see about a 50% split, it's gradually moving closer to the 80% on the smooth and 20% on textured.

DR. LEWIS: Okay.

Yes, Dr. Ballman.

DR. BALLMAN: So, in the long-term post-approval studies that are ongoing, what are the differences between what's captured in the questionnaire and what's captured in the office visit?

MS. d'INCELLI: So, for Sientra's study, there is a questionnaire annually, so every year questions are collected. The patients will complete symptoms, quality of life questions, measures, diagnosis, basically a full medical history, what medications they're taking. Those are collected annually from patients in questionnaires. When they are in for an office visit, there's additional collection of those endpoints as well as measures of local breast complications, so they're assessed for capsular contracture. However, even when the patients do answer their questionnaires remote online, those questions are asked as well, so the local breast complications, capsular contracture, etc., are collected.

MS. CARTY: Kelly Carty, Allergan.

We have a very similar design. The one thing I would add to that is when patients come into the office, the surgeons confirm connective tissue diagnoses.

DR. LEWIS: Yes, sir.

MS. DAURIA: The same for Mentor.

DR. ANDERSON: I have two questions, one for Mentor and one for Sientra. In the Mentor presentation you showed us those pictures of the different types of texturing methodology that was used, how different they looked, and that was very striking. I'm curious. Texturing is also used in other types of implants, like orthopedic implants. I think it's all smooth with pacemakers. Is there any comparison with any other implant in the body that might give some insights into this?

MS. DAURIA: Dr. Canady.

DR. CANADY: John Canady, medical affairs for Mentor.

Just from a manufacturing standpoint, I'll speak to ours. It's an imprinted process that goes before the silicone is cured. So, for other metals, other materials like metals or other types of things, it's not a similar process.

DR. ANDERSON: So there really aren't -- there is no analogy to this, to the disorder

that seems to be linked to the texturing outside of breast implants; is that our understanding?

MS. DAURIA: Not that we can speak to from our own studies.

MS. d'INCELLI: From the literature, there are several reports of ALCL cases in other medical devices, if that's what you're asking.

DR. ANDERSON: Yes.

MS. d'INCELLI: Yeah, in many. There's ocular, lap band, catheter, pacemakers, knee, and I believe hip. So, there are case reports in quite a variety of literature of this occurrence in other medical devices.

DR. ANDERSON: Other devices, texturing wasn't necessarily part of that?

MS. d'INCELLI: Not necessarily.

DR. ANDERSON: Okay. I also have a question about in the Sientra presentation you had one slide where you said breast implant illness, and you showed us in text that you provided some comparison between the implant and control group, and you said there were no statistically significant differences. You showed us no data, so we couldn't tell if it was powered adequately to make some type of comparison like this. Is this going to go into the peer-reviewed literature so it can be examined?

MS. d'INCELLI: Absolutely. We have our full dataset, and we shared it with FDA, and we will share this. In the interest of brevity, we didn't -- we couldn't include everything we wanted to. I can ask Maggi Beckstrand to come and speak up. She's our biostatistician.

DR. LEWIS: I think we need to move on.

MS. d'INCELLI: Okay. Okay, so we do have it.

DR. LEWIS: All right, we need to move ahead to the next phase, so thank you all for participating, and thank you for your presentations.

We'd like to move to a detailed presentation from the FDA, from Karen Nast and

Dr. Michael DeLong.

MS. NAST: I'm Karen Nast, a nurse consultant in the Division of Postmarket Surveillance in CDRH. I'm going to provide an overview of the MDR data for BIA-ALCL and breast implant illness symptoms.

Since September 30th, 2017, 246 new MDRs were received resulting in a cumulative total of 660 MDRs for BIA-ALCL. This total includes all MDRs that contain the term ALCL or variations of it in the event narrative. BIA-ALCL MDRs are counted for those reporting an ALCL diagnosis or treatment or confirmed pathology or cytology test or ALK or CD30 biomarkers.

FDA staff further analyzed the 660 cumulative MDRs. Duplicate reports were excluded and supplemental reports were reviewed. We believe this dataset more accurately reflects the number of BIA-ALCL reports. These data reflect a total of 457 distinct MDRs for BIA-ALCL. There were 12 death reports representing 9 patients. All 457 reports include the implant fill type. There are 274 reports for silicone gel-filled implants and 183 reports for saline-filled implants. This is a late disease, and on average, most patients present 8 to 10 years later.

There are 310 reports for textured implants and 24 reports for smooth implants, and this is at the time of diagnosis. In almost 30% of the reports we don't know the surface type; it wasn't reported. In most of these reports, the full patient history of prior implants, whether textured or smooth surface, is unknown. Also unknown is the total number of textured surface breast implants implanted versus smooth surface implants to know if there is a higher rate of BIA-ALCL with one implant type versus another implant type.

Due to missing or incomplete data, the distribution of patient and device characteristics in both datasets may not accurately be reflected. However, the FDA believes that the data in this table more accurately reflect the number of MDR reports of BIA-ALCL

cases: 457.

FDA is not aware of any MDRs reporting ALCL in devices other than breast implants. ALCL has been associated with devices other than breast implants in the literature. We are aware of less than 10 case reports in the literature.

FDA conducted a query of the MDR database for all reports entered between January 1st, 2008 and October 31st, 2018, referring to a saline- or silicone-filled breast implant with search terms used to represent the various symptoms patient groups refer to as breast implant illness. The search terms were taken from the list of symptoms on the website Healing Breast Implant Illness.

The search included over 80 terms, and the resulting 1,328 MDRs contained at least one term. A majority of these reports were submitted by voluntary reporters. Voluntary reporters include healthcare professionals, patients, and consumers. There were similar numbers of reports for saline and silicone gel-filled implants. There are 1,311 injuries and 8 death reports describing 4 patients. It is not clear that the deaths are related to BII. These reports are included because they contain the keyword search. The most commonly reported symptoms included fatigue, brain fog, rash, joint pain, and memory loss. Some reports concerned health issues of children born to women with breast implants, leading to reported patient ages ranging from 9 to 76 years of age. The time to reported onset of symptoms ranged from less than 1 month to over 38 years. Out of the 1,328 reports, less than half provided an explant date, and of those, the time to explant ranged from less than 1 month to over 40 years, and 101 of those MDRs reported improvement in symptoms after explant.

Incomplete information provided in MDRs regarding what patients perceived as improvement in symptoms or the time course for improvement prevented further analysis. It is not clear that current routine reporting accurately captures information on

explantation due to BII.

Although MDRs are a valuable source of information, this passive surveillance system has limitations including underreporting, data quality issues like the potential submission of incomplete, inaccurate, untimely, unverified or biased data, limitations of the MDR regulation. A lack of MDRs does not necessarily mean there are no problems. It is not possible to definitively determine a causal relationship between an event and the device based off MDR data alone.

Finally, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential underreporting of events and lack of information about the total number of devices. These data do not represent a complete understanding of breast implant illness, and these reports alone do not demonstrate that breast implants are causing the symptoms of breast implant illness.

The Panel will be asked to discuss methods for assessing and addressing breast implant illness symptoms. The Panel will also be asked to make recommendations regarding next steps for the characterization of BIA-ALCL incidence and these risk factors.

Dr. DeLong will now speak about breast implant illness symptoms reported in post-approval studies.

DR. DeLONG: Hello, everybody, and good morning. I'm Michael DeLong, a medical officer in the Division of Surgical Devices, and I'll be presenting the information that we have from the manufacturer post-approval studies regarding symptoms similar to the BII reports.

In preparation for this meeting, we asked each manufacturer to provide information regarding symptoms of breast implant illness from their post-approval studies. This table illustrates the post-approval studies that are most relevant to BII endpoints. You will notice that there are two redesigned studies, one for Mentor and one for Allergan, to replace the

original large post-approval studies for these manufacturers. Recall that the reason that these studies were redesigned is because of low patient follow-up, which was discussed in FDA's General and Plastic Surgery Advisory Committee held in 2011.

Please note that in order to obtain marketing approval, each manufacturer was asked to perform a core study which involved follow-up for several years before device approval and continued patient follow-up after device approval, so that patients were followed for a total of 10 years. Ideal only manufactures saline implants, and so the Ideal post-approval requirement was just this continuation of the core study to 10 years.

The red boxes on this slide indicate the studies that are currently ongoing. The other studies have either been replaced or have been completed. Each manufacturer has one ongoing study with endpoints relevant to BII.

In November of 2018 the FDA requested that sponsors submit the most current systemic symptoms data from their post-approval studies. Each manufacturer submitted data from a different study. It is very important to note that each of these studies have substantially different protocols preventing any comparisons between studies. Additionally, a basic understanding of each protocol is important to contextualize the presented data.

On this slide we have highlighted the studies that were referenced or submitted in response to FDA's request. Recall that the red boxes are around the currently ongoing studies. Allergan submitted data from their ongoing breast implant follow-up study, which is the redesigned large post-approval study. Mentor referenced data from their original large post-approval study prior to the redesign. Sientra referenced data from their completed core study final report. And Ideal submitted data from their ongoing core study continuation, which is their post-approval requirement.

This table provides a brief overview of the study differences. As you can see, the protocols and patient populations are sufficiently different that no comparisons can truly be

made between studies. We will start with Allergan's breast implant follow-up study. This is the redesigned version of their original large post-approval study that was replaced and redesigned after the 2011 Panel meeting.

The BIF study protocol was approved in August of 2015. The study protocol did not involve enrollment of new patients. It consisted of selecting 2,000 silicone and 257 saline Allergan implant patients from the original large post-approval study cohorts to continue to 10 years. Because the protocol intentionally selected patients from the original cohort who were compliant with follow-up, there's guaranteed 100% 4-year follow-up in both cohorts. Additionally, this selection process does not necessarily eliminate follow-up biases; 95 different symptoms are included in the annual patient questionnaire, and we will focus on the 19 that are most consistent with the BII MDRs.

The study was designed to saline implant patients as a control group for assessing the incidence of these symptoms. However, because patients with saline implants have also reported BII-related symptoms and represent roughly half of the MDR reports, we will present the incidence rates in both cohorts separately without a comparison group. The relationship between these incidence rates and national norms is unknown.

Incidence percentages are reported in the BIF study as the patients who did not have the symptom at baseline who report that symptom at any time point after study initiation. Therefore, the denominator for these percentage calculations is the original study cohort regardless of follow-up and may underestimate true incidence at later years as patients are lost to follow-up.

This chart displays the symptom data from the silicone cohort, separated by indication. This information is found in the publicly available Executive Summary on page 21. All patients in this cohort have reached at least 7 years since implantation, and there's a 78% follow-up rate. The highlighted fields are all groups with at least 10% incidence,

which are found to include several symptoms that may affect a patient's quality of life, such as arthritis and joint pain or confusion and memory loss. Again, the relationship of these incidence rates to national norms is unknown.

This slide presents the data from the Allergan saline cohort who have all reached at least 7 years since implantation with a 78% follow-up rate. Again, all symptoms of greater than 10% incidence are highlighted, and again, the relationship of these incidence rates to national norms is unknown.

In response to FDA's 2018 request, Mentor referenced data from their original large post-approval study, not the redesign after the 2011 Panel meeting. This is because after having inadequate follow-up in the original large post-approval study, Mentor's redesigned study was a new enrollment study. Due to ongoing enrollment, this study is still in its infancy with most patients not even at 1-year follow-up by the time of the Agency's request.

Additionally, Mentor recently received a warning letter for inadequate enrollment in one of the cohorts in this new enrollment study. Therefore, Mentor chose to reference the 7-year data from their original large post-approval study.

This study is similar to Allergan's study in that saline implant patients were used as the control group. So, again, the cohorts will be presented separately without a comparator because patients with saline implants have also reported these symptoms in the MDRs. The symptoms collected differed from those in Allergan's study, but again, we will present the 12 symptoms that are most relevant to the MDR reports.

This slide presents the data from the silicone implant cohort, available in the Executive Summary on page 22, who have all reached at least 7 years since implantation with 15% follow-up rate. Again, all symptom groups with greater than 10% incidence are highlighted, including symptoms consistent with MDRs that may be concerning for patients,

such as arthritis and joint pain or persistent fatigue. Again, the relationship of these incidence rates to national norms is unknown.

This slide presents the saline cohort who have all reached 6 years since implantation with 12% follow-up. Again, fields with greater than 10% incidence have been highlighted, and again, the relationship of these incidence rates to national norms is unknown.

In response to FDA's 2018 request, Sientra referenced data from their completed core study continuation rather than their ongoing post-approval study. Sientra's ongoing post-approval study was only at the 2-year time point and also recently received a warning letter for insufficient follow-up in this study, so they reference the 10-year data from their completed core study continuation with 51% final compliance with the symptom questionnaire. Again, we focus on the 13 endpoints most related to the MDRs. However, it is important to note that most core studies are focused on local complications, and the reporting for systemic symptoms is not always as complete in these studies.

In the Sientra study, no symptom was present with an incidence of 10% or greater. However, these data are from a core study and may be less complete.

In response to FDA's 2018 request, Ideal submitted data from their ongoing core study continuation. This was their post-approval study requirement. It is important to note that Ideal only manufactures saline implants, and they are indicated only for augmentation and revision augmentation. Additionally, their study protocol did not collect data on patient symptoms and only required the enumeration of all patients referred to a rheumatologist, who were not referred at baseline, at Years 1, 2, 3, 4, and 7.

All patients in the Ideal study have reached 8 years since implantation with 94% follow-up rate. The cumulative totals for new referrals to rheumatologists are 7.8% of the primary augmentation group and 9.7% of the revision augmentation group. It is unknown how these incidence rates relate to national norms for similar populations. Again, the

protocol did not require collection of symptoms data, so symptom incidence is unknown.

In conclusion, the data from the PAS are limited by follow-up and reporting issues. There's significant differences in study protocols that preclude any comparisons between separate studies. However, symptoms consistent with the MDR reports have been observed in these studies, although the relationship between these incidence rates and national norms is unknown.

Thank you.

DR. LEWIS: Do you have a further presentation?

(Off microphone response.)

DR. LEWIS: All right, we have the opportunity for clarifying questions from the Panel.

MS. PAWELSKI: Lynn Pawelski.

This question is for Karen Nast. When you show the MDR numbers, do those include those submitted as individual MDRs and the summary reporting from manufacturers?

MS. NAST: Thank you. The MDRs for ALCL are individual reports because ALCL is not allowed to be submitted through any other method. The MDR reports for BII are also from individual reports. We consider these events unusual or uncommon, and so they should be reported, would be reported, as individual MDRs.

MS. PAWELSKI: So, it's a complete representation of what the manufacturers submit, everything that you get?

MS. NAST: As far as we're aware, yes.

DR. LIPPMAN: I'd appreciate some kind of clarification as to what efforts you can go to, to obtain what I would consider to be some sort of control group. I mean, short of a randomized prospective trial, it seems to me there must be other kinds of devices or other kinds of things that the FDA monitors in which one could explore the incidence of these

subjective complaints. I'm not talking about the lymphoma. I think it's very tricky. I'm very familiar with a large series of studies involving aromatase inhibitors, which have apparently major subjective complaints associated with them, and I'm trying to understand can you get other information from studies that you deem reliable for other kinds of comparator groups of women to get some notion as to what we're really talking about here?

DR. DeLONG: So, a couple different approaches have been attempted. This is one question, I think, that we would also ask the Panel is, what is an appropriate control group because the identification can be difficult. The initial studies use saline implant patients as the control group, as we discussed, but if patients with saline implants are reporting these symptoms, they may not represent an ideal control group for investigating these symptoms.

Some of the redesigned post-approval studies are now using other cosmetic surgeries that do not include an implant, but it can't necessarily be assured that those patient populations are identical or similar to a breast implant patient in terms of age, demographics, and other behavioral patterns. So, it is a complex issue, and it's one, I think, the Panel could be very helpful in discussing. Thank you.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: Just to further with that, Dr. DeLong, in the Danish study in 2007 they had 3,000 breast implant patients and 8,000 other plastic surgery patients all matched for age and gender, and most of those were breast reductions, liposuction and so forth, and the differences in defined connective tissue disease was the same in both groups and with the national population figures, the prevailing Danish registries.

But the interesting thing I always thought in that study is that there was what they called non-diagnosable rheumatism complaints, and it was identical in both groups. And that's the only data that I'm aware of where we really have a feeling for a group that was matched from something that was not getting a device, and it was very telling that the

numbers were quite statistically compelling.

DR. LEWIS: Yes, Dr. Leitch.

DR. LEITCH: For Dr. DeLong, on the Sientra data you said that they were a continuation of the core study and the symptoms were all less than 10% and you said that may be less that complete; what did you mean by that?

DR. DeLONG: In general, the core studies are premarket studies designed to assess the safety and effectiveness of a device before approval, and so they focus -- they typically run to about a 3-year time point before their device is considered for approval, and so they tend to focus on local complications and several risks, and they may not be powered or designed necessarily to study specifically rare adverse events such as the neurologic or connective tissue disorders. So, the postmarket studies were often like the large post-approval study, more focused on those endpoints. And so, because it was a core study that was referenced, we don't know that it was -- it wasn't -- the rare endpoints were not necessarily the primary focus of that study, if that makes sense.

DR. LEWIS: Dr. Li.

DR. LEITCH: But they have to have -- if they have the questions, why wouldn't it be and what was the duration of follow-up of that?

DR. DeLONG: The duration of follow-up for their study was 10 years because it was the completion of the core study. The questionnaires just may not have had as many questions, if that makes sense.

DR. LEITCH: But for an individual complaint, if it were less than 10%, the question was asked, right?

DR. DeLONG: Correct. That is correct.

DR. LEWIS: Dr. Li.

DR. LI: Yes, I have a couple of questions for either Ms. Nast or Dr. DeLong about the

MDR, itself. In other device areas we estimate the number of MDR reports versus the actual number of failed devices is very small, sometimes maybe only 1%. So, do you have any feel for the MDR data for breast implants, what percentage of MDRs are reported versus, say, the number of reconstructions or the number of reoperations?

MS. NAST: We're not able to gather incidence rates from MDR data alone to choose several factors we've gone through in the presentation, including underreporting --

DR. LI: Well, how about -- excuse me, I'm sorry to interrupt, but let's say there's -- we saw one number this morning, there was 85,000 reoperations, so -- versus 85,000 reoperations in a single year, how many MDR reports would you get? If you don't know, that's okay. It's a question just to see -- just to try to get some feel for the amount of reporting that actually gets done.

MS. NAST: It's hard to say. We do get mandatory reports that meet the criteria for malfunction, serious injury, or death. We also receive voluntary reports. I don't think we can say how many reports per surgeries we get.

DR. ASHAR: You know, what we could do is we can look up the number of total MDRs that we receive annually for breast implants and provide that to you at the next break, and that perhaps will help address the question so that you may be able to make the comparison to the number of reoperations that you're aware of from the literature and other --

DR. LI: That would be fine. I just want to get a feel for is the number as small for breast implants as it is for every other device. Sorry.

DR. ASHAR: Right. Yeah, we'll come back to you with that information.

DR. LI: Okay. And then a quick follow-up question on that. Over the 457 cases of ALCL that you reported, over what time period were those collected?

MS. NAST: I don't believe there was a beginning time period. Those are up to date.

DR. LI: But going back how far, I guess.

MS. NAST: We received data, I think we began receiving MDR reports in the 1990s. I don't think we limited the beginning of our data.

DR. LI: Okay, I was just trying to get -- I was just trying to get a feel for is the number -- it seems like the number of reports has changed, increasing with time, and I was just trying to get a feel for how many reports you're actually getting; 457 sounds like a lot, but if it's spread over 15 years, it's not so much. So, I'm just trying to get a feel for the seriousness of the issue.

DR. ASHAR: I think what we can do is we can give you what we've had, is the increased number of cases over the past several years; we've had an increased number of cases since our 2011 report, you know, announcing that this was the finding and every year it's gone up annually. So perhaps that will be informative. Now, when the first earliest case was, we would have to also go back and check in our records, but this is our full understanding of BIA-ALCL from our MDR database.

DR. LI: Yes. And then one last quick question. We've heard that there's 457 reports of ALCL. We've heard from each manufacturer that the number of cases they know about actually are quite small, four or five. So, in your MDR, could you identify and actually break down whose implants were actually involved in each ALCL case? Because right now I've got 457 implants of unknown supply, and then each manufacturer is saying kind of it's not us.

(Laughter.)

DR. LI: So, I'm trying to figure out whose implants these are.

(Applause.)

MS. NAST: Thank you for your question. Our data oftentimes is not complete, so I don't believe we have complete data for 457 reports. I also want to add that we do receive data that is outside of the U.S. That is reportable to us also. So, we receive data for devices

in the U.S. as well as outside of the U.S.

DR. LEWIS: Dr. Sandler.

DR. SANDLER: Thank you.

A couple of quick questions. One is are there any known or validated biomarkers for BII, and has there been any attempt to identify serological measurements that could be strongly associated with the symptoms that are being reported?

DR. DeLONG: As far as I know, the -- I mean, there's no established diagnostic criteria. We do have an expert from Canada who's going to be talking about ASIA syndrome, and he's done some investigating in terms of different biomarkers of laboratory tests that may be associated with that condition. It may be applicable to the study of BII.

DR. SANDLER: Thank you.

And one other quick question. One of the things I was most struck by, as I was reviewing all the literature that FDA supplied, is how frequent the rupture rate is. I'm just surprised that so many times the device sort of fails fundamentally and I just -- I don't understand that and I was wondering if FDA -- or maybe I should've asked the manufacturers -- can explain what the mechanism of rupture is and why the devices aren't designed in such a way so that the risk of rupture is small.

DR. ASHAR: I agree, that would be probably the best -- more appropriately directed to the manufacturers.

DR. SANDLER: So, FDA has no opinion on that?

DR. ASHAR: We provide mechanical testing or require that the manufacturers perform some extensive mechanical testing prior to marketing of their device, and that information is contained in the summary of safety and effectiveness that was included as an appendix in your advisory committee pack. And so that includes as detailed information as we can provide regarding the components used to create the device, as well as the bench

testing performed, as well as any animal testing and all of the human clinical testing that was done premarket.

DR. SANDLER: Thank you.

DR. LEWIS: Dr. DeLong, in the data from the FDA and the MDR reporting, you cited approximately a 6% incidence of ALCL with smooth implants. As far as I know, in the PROFILE data to date, if patients who had a previous implant prior to a smooth implant are excluded, there are no incidences of ALCL with smooth implants. So, while it's not a huge difference, I think it's an important difference to know if the zero number is correct or if the low incidence is correct. Can you clarify that?

DR. ASHAR: We are fortunate enough to have the -- Dr. Pusic, who heads up the PROFILE registry, and Dr. Clemens speaking later on today, and so they may be able to tell you specifically about the information obtained from the PROFILE registry.

DR. LEWIS: Thank you. Yes.

DR. JAFFE: Yeah, I have a question about assessing the incidence of the breast implant-associated ALCL. A problem in some of the meetings that I've attended in the past is that a lot of patients with seroma have draining of the seroma fluid, and the fluid is not sent routinely to pathologists for cytologic evaluation, and I'm wondering if the FDA has played a role in trying to correct that issue and whether there's been a change in practice in terms of assessing patients with clinical seroma.

DR. DeLONG: So, the FDA is hopeful that we can spread awareness of this disease process. We've recently released a letter to healthcare providers, and we work very closely with the professional societies trying to make sure, not just in plastic surgery, but any professional society that might take care of a patient who develops ALCL, and our hope is that we can increase awareness of this diagnosis so that providers are informed and patients are informed of the steps that would be necessary to take to try and achieve a

diagnosis or rule out the disease.

DR. LEWIS: Yes, Dr. Rogers.

DR. ROGERS: I have a question about BII and the wide range of ages that we've seen in some of the data, very, very young women to older women, and is there any correlation in the reporting based on age, or is it mostly linked to the length of the implant being in place?

DR. DeLONG: I'm not sure that we're aware of any correlation. We can try and look into that, but I don't know that we have that kind of analysis that would link the patient age to the symptoms of BII.

DR. ROGERS: This is just getting back to predisposing factors that might influence development of some of those. And it was striking to me that the indication for the implant also was correlated, seemed to be -- the incidence of BII seemed to be different based on the indication for the implant, and there's quite an age stratification for that. So, I was just curious about whether any of these reports have been looked at in terms of the demographic of who's reporting.

DR. DeLONG: Right. And some of that is confounded because the revision groups are likely to be older, but they also had prior implants, and so they're likely to have been exposed to implants for longer. So those two variables are often shown hand in hand.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: One thing I would say about the question that Dr. Rogers just asked is that a lot of the reconstruction patients could be taking aromatase inhibitors, which have similar symptoms as the prominent symptoms that are listed there, so that could be a factor in those patients.

My question was going to be related to compliance and what are your thoughts about compliance, is it at all related to the financial support that is given to the -- by the

companies to encourage compliance? Because it was mentioned that some of them do give incentive for compliance.

DR. DeLONG: Is your question whether providing a financial incentive increases patient compliance with a questionnaire?

DR. LEITCH: Right, has that been shown?

DR. DeLONG: That might be a question the manufacturers would be able to answer in terms of what financial packages they provide and what they've seen for compliance.

DR. ASHAR: And I can add that, you know, we do several things to try to think about innovative ways to promote compliance with a study so that we get meaningful data at the end of the day. I have to say that probably companies are much more compliant in getting their patients to follow up in the premarket when a premarket approval is being sought, and in a postmarket arena, we're not as successful. What those reasons are, we're not entirely sure, but there are many strategies that FDA proposes when working with manufacturers.

DR. LEWIS: Yes, Dr. White.

DR. WHITE: Yes, thank you.

I just want to get -- see if I was clear in my understanding that you -- this is to Dr. Karen Nast commented that they were not aware of other ALCL diagnoses with other implant devices, but one of the industry representatives had mentioned some other cases of ALCL reports. Did I get that correct that you're not aware of these cases?

MS. NAST: That's correct, we are not aware of any cases of ALCL in devices other than breast implants being reported through our MDR system. However, we are aware of less than 10 cases that were reported through the literature.

DR. LEWIS: Yes, Dr. Burke.

DR. BURKE: I just wondered if there have ever been any studies to see the

components of the seroma fluid and if there are any non-biologic, in other words synthetic, parts of the synthetic -- what synthetic particles or potential toxins might be in the serotonin fluids.

DR. ASHAR: Our current recommendations regarding BIA-ALCL diagnosis focus primarily on how to diagnose the disease and sending the fluid and fibrous -- the capsule, for pathology evaluation. This Panel, if it felt appropriate, could make recommendations about additional tests that might be done on the tissue surrounding the breast implant.

DR. LEWIS: Dr. Li.

DR. LI: I just had a quick question -- a quick answer to Dr. White's question. I actually just ran across this weekend an odd article. In February, there was a report of a silicone gluteal implant that developed the same lymphoma. It was the only -- it was a single case report, but it was a silicone textured gluteal implant.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: That was not histologically confirmed in the buttock.

DR. LI: Understood.

DR. McGRATH: The patient had metastatic ALCL and had buttock implant. There's no proof that the buttock had any ALCL, and the buttock implant had only been there for 1 year.

DR. LI: I completely agree with you. I was just remarking that there was a report.

DR. LEWIS: Are there further questions?

Yes, Dr. Gallagher.

DR. GALLAGHER: So, this is Colleen Gallagher.

I'm just wondering, since it seems that so much of the effort of education and everything has gone to the board-certified plastic surgeons, how many of these surgeries are done by board-certified plastic surgeons compared to those done by general surgeons

or others?

DR. DeLONG: I don't know that we necessarily know those numbers, at least not off the top of our head. The American Society of Plastic Surgeons provides their statistics in a survey report every year. There are also things like the American Board of Cosmetic Surgery, and I believe their members also perform these procedures, but I'm not aware of what their incidence rates are.

DR. LEWIS: Dr. Portis, did you have a question?

DR. PORTIS: Yeah. I wonder, with the MDR, I know that there's some mandatory reporting, but do you have -- I know this is a hard question to answer, but what about patients who don't know about the MDR and don't know about the information on FDA's websites? Like how do we find those people, and what percentage do you think we are actually reaching?

MS. NAST: I can say that we have seen a definite increase in voluntary reports in the past few years. I think some of the reasons for this are definitely the increased social media aspect that's been increasing awareness. We definitely receive many voluntary MDRs, and we value those greatly.

DR. PORTIS: Does FDA make any effort to reach more patients to let them know of the concerns and that we want more reporting?

DR. ASHAR: With respect to BIA-ALCL specifically, in the past couple of months we recently issued a letter to healthcare providers, and this was different than the letter that we issued back in 2011. The one in 2011 just went to plastic surgeons, and on the advice of patient groups that came and talked to us, we issued a second communication. This went to all healthcare providers that we could think of that would touch a patient that potentially would have breast implants during her lifetime, to promote awareness. But more definitely it could always be done, and we hope that forums like this will cause individuals to go back

to their communities and their societies and communicate this risk and advise people to report adverse events.

DR. LEWIS: All right, we need to move ahead with the next phase of the program. I thank the FDA for their presentations.

We'll move into the public hearing now. We'll proceed with the first portion of the public hearing, there being three more opportunities, obviously, during the 2 days. For the record, all Panel members have been provided with written comments received prior to this meeting for their consideration. During the Open Public Hearing, public attendees will be given an opportunity to address the Panel, to present data, information, and their own views relevant to the meeting agenda. I would also like to urge those who speak to include in their presentations, whenever possible, their recommendations for actions which are needed, they feel, to correct the problems which they are complaining about, so that the Panel has a clear idea of what they feel is needed.

Commander Garcia will now read the Open Public Hearing disclosure process statement.

CDR GARCIA: Thank you, Dr. Lewis.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA

encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Dr. Lewis.

DR. LEWIS: The FDA and this Panel place great importance on this Open Public Hearing process in order to adequately allow those who are speaking to fully address their complaints and shortcomings of the system. The insights and comments provided can help the Agency and this Panel in their consideration of the issues before them.

That said, in many instances and for many topics, we know that there are a wide variety of opinions, often strongly held. One of the goals today is for this open hearing to be conducted in a fair and open way, where every participant is listened to carefully, and the Panel anxiously is looking to hear from you and hear your views, and we wish everyone to be treated with dignity, courtesy, and respect. People will speak only when recognized by the Chairman, and it's important that we maintain a strict limitation on the 3 minutes because we have 22 people signed up for 1 hour.

And so, to be fair and to give an opportunity for equal presentation time to the later participants, it's essential for everyone to limit themselves to their 3 minutes. We ask each presenter to speak clearly into the microphone, and we will provide an accurate transcription of the meeting. Please identify yourself and your association clearly. If the speaker goes beyond the 3½ minutes, we will generally shut off the microphone in order to move to the next person.

We also note that there are -- in order to be efficient, we ask that the speaker, when one person is speaking, the next speaker please position themselves nearby so that they can immediately begin their presentation on completion of the first speaker's comments.

The first speaker today is Dr. William Adams from the FORCE Organization. Would

you step to the microphone and begin your presentation?

DR. ADAMS: Thank you. Good morning, I'm William P. Adams, Jr., a board-certified plastic surgeon and Education Commissioner of the Aesthetic Society, Associate Professor of Plastic Surgery at UT Southwestern Medical Center in Dallas, and Chief Medical Officer of the Plastic Surgery Channel. I have no other financial disclosures for this presentation.

Education and training of surgeons is a primary function of the Aesthetic Society, and since breast implant-associated ALCL was first recognized, the Aesthetic Society has been educating our members through clinical education and online accessible treatment guidelines and FAQs. Importantly, current data in epidemiology on ALCL has demonstrated at least eight instances of case clusters in geographic distributions that indicate an infectious trigger or cause. Furthermore, this is an implant surface area issue currently only occurring in patients with a history of textured devices and, more commonly, in larger surface area textured implants providing an environment for exponentially higher bacterial implantation and sequestration. A similar bacterial-mediated adverse event pathway has been confirmed for the most common risk of breast implants, called capsular contracture.

Over the past 20 years we have learned that surgical technique is critical, and I've spent much of my career researching and educating surgeons on techniques to reduce the bacterial load around implants during surgery. Techniques including the 14-point plan have reduced documented risk of capsular contracture from 50% 30 years ago to less than 1% in the past 5 years. We are confident that these bacterial load-reducing best practice techniques will have similar risk reduction of ALCL for patients.

Clinical evidence for this risk reduction in ALCL includes a study published in 2017, that you see here, by eight global surgeons using the same 14-point plan at the time of surgery and 42,000 macro-textured implants. The expected number of ALCL cases was 14; yet, the actual number of cases in this study was zero.

And, finally, with regard to joint patient and physician education, working with advocates Jamee Cook and Terri McGregor, the Aesthetic Society and the Plastic Surgery Channel have featured ongoing collaborative educational dialogue between patients and surgeons. We have produced two separate programs to date: the first, a roundtable discussion including three ALCL patient leaders to create awareness and education on ALCL, and a second in-depth PSE deep-dive program that was just premiered last week, focusing on roundtable education on the key BII issues, best informed consent and communication practices for surgeons and patients. The feedback has been fantastic, and we intend to continue these patient-physician educational programs, and the main connected parties are currently working to set up a collaborative community per FDA guidelines.

Thank you all for your time today.

DR. LEWIS: Christina Avila.

MS. AVILA: Hello, my name is Christina Avila. I have traveled from San Jose, California, by my own accord to speak before you today. Thank you for hearing me.

When I was diagnosed with Stage III breast cancer at age 38, as I joyfully raised a long-awaited 2-year-old, I put all my faith and trust in my doctors and went down the pathway before me. In a time of intense shock and vulnerability, many other survivors like me feel they were pushed down a path where they were assured that implants were safe but told little to nothing about their many risks. Instead, they were often told that they were too young not to get implants or that they would be left deformed, depressed, with low self-esteem, not feeling whole, complete, and the list goes on. Many felt they were not presented another option, and sadly, I have heard too many saying I thought we had to do it. I will speak to you on what we should have been informed of but were not.

Patients should be informed that the standard practice of radiating either expanders or implants is contraindicated by the manufacturers. And now I've read too many cases of

fellow survivors who were radiated with silicone above their lungs, receiving new diagnoses of small cell lung cancer. Could I be next?

We should be told expanders are not to be left in for longer than 6 months. Patients should know that if radiation is part of their treatment, they will almost always develop capsular contracture and possibly have issues with any incision made to that area healing.

We should be told that beginning reconstruction at the start of our treatment often leads to complications that cause delays in our cancer treatment. This not only compromises our health but also our chances of survival.

We should be told that a successful outcome will require multiple surgeries in just a few years' time during and following our treatment and that each of these additional surgeries may trigger PTSD.

We need to be informed that we will be left with a concavity if our implants are ever removed.

Over and over, we are told there are not studies that show implants cause health problems, but rarely if ever are we told there are no valid unbiased studies. How many survivors progress to Stage IV after getting implants? Women like me, who would rather be alive than have something that looks like boobs, need to know these numbers. I am sickened that during the 11-year ban, silicone implants were only allowed to be placed in one population, the most vulnerable one, breast cancer patients.

(Applause.)

MS. AVILA: Sorry, am I -- is my time up? People are clapping, but my time's still going. Breast cancer patients. Why were those of us who just finished fighting for our lives the only ones who could still be implanted with devices deemed unsafe for everyone else? All women deserve to be fully informed on what I've shared today. They deserve to know their risks; they deserve true informed consent. Since learning about breast implant illness,

I have met thousands who would've never gotten implants had they received the proper informed consent. So many of them say it was their breast implants that caused sickness and suffering that far exceeded their cancer treatment, including chemotherapy and radiation. This speaks volumes.

My name is Christina Avila. Please know that when you hear my voice, you are hearing the voice of tens upon tens of thousands of women. Thank you for hearing us.

DR. LEWIS: Thank you.

Dr. Anu Bajaj.

DR. BAJAJ: I'm a board-certified plastic surgeon who performs both cosmetic and reconstructive breast surgery in Oklahoma City, and I have had breast implants since 2003. While I am a plastic surgeon, I have never been an advocate for breast implants. Rather, I come as an advocate for my patients and for patient choice.

My father is also a plastic surgeon who's been in practice since 1972. His experience in the '90s led him to distrust breast implants and their safety.

During the past 20 years I have also observed my own share of adverse consequences of implants, which have included rupture, infection, and capsular contracture. At times, as a young surgeon, I had thought, why would anybody want breast implants, and then I chose to get breast implants. I chose to get implants because I had felt self-conscious about my lack of breast development. I was tired of wearing padded bras and having clothing that did not fit. Once a woman in my 30s, after having gone for a run, I was told that I looked like an 11-year old boy. So, I got breast implants, and I have never regretted this decision, and I feel very confident and happy.

Both my cosmetic and reconstructive patients have similarly told me that they are happy with their implants and do not regret their choices. Their comments have included how much they like their breasts or how much better they feel, and they never realized it

would affect them so much.

Numerous studies and my personal experience and my own patients have shown me that they do have a high satisfaction rate and can benefit your quality of life and self-esteem.

My sisters also have had breast implants and have had very different experiences. One sister switched from silicone to saline because she was concerned about her health as well as the risk of silent rupture. The other sister had her implants removed because her body had changed.

Every surgical procedure, including the placement of breast implants, has risks and benefits. Some patients will benefit, and others may not. Like my sisters and myself, implants aren't for everyone. Our job as physicians is to listen to our patients, educate them about risks and benefits, and help them make the decisions that will be best for them. Our patients are capable of understanding these complications and risks and each individual will need to make the choice that best suits her values.

However, we need the data and information to provide our patients with the best and most up-to-date information available. We also need to educate our patients about the importance of annual follow-up with their plastic surgeons so that we can monitor for these adverse events. Rather than taking away choices from women, we should arm them with information so that they can make the right decision for themselves.

Thank you.

DR. LEWIS: Thank you very much for your comments.

Dr. Bradley Calobrace.

DR. CALOBRACE: Good morning and thank you for allowing me to present to the Panel. My name is Dr. Brad Calobrace. I'm a plastic surgeon, board-certified, in Louisville, Kentucky, over the last 22 years. I'm also Clinical Professor of Surgery at the University of

Louisville and at the University of Kentucky, so I've been highly involved in education of plastic surgeon residents and actually initiated a breast fellowship within my practice. I also publish and lecture extensively on the subject of breast surgery and probably most significantly on the issues related to breast implants. And I have no financial disclosures.

As a member of the Aesthetics Society and as the chair of the BIA-ALCL task force over the last year, and after extensive review of the current world literature, our task force put together a large amount of material to physicians and patients which are educational materials to help them. They also include a semiannual advisory update that we do in conjunction with the ASPS.

Additionally, in January 2018, in an issue of *Aesthetics Surgery Journal*, I published an article called the "Long-term Safety of Smooth and Textured Silicone Breast Implants." This article reviewed the data from all five core FDA breast implant clinical trials in which all demonstrated long-term safety of smooth and textured implants in those studies.

The limitations of many of these clinical trials is that struggle to meet the levels the FDA required for patient follow-up. In my experience, patients who are doing well often just don't want to come back for follow-up, and this can be a real challenge that we all face, but we desperately need this information. To improve follow-up in future clinical trials, our task force has recommended the use of technologies, like maybe mobile apps and digital health, to collect and analyze data to improve patient follow-up.

Having placed over 15,000 breast implants, I have observed there's no one perfect implant choice. Smooth and textured, shaped and round implants, each provide benefit to address challenging anatomical issues in both aesthetic and reconstructive breast surgery patients, and the implant choice must be balanced against the risks associated with each of these.

Furthermore, I occasionally use textured implants, I use evidence-based medicine for

that, and the data has demonstrated bacteria as the probable cause of ALCL. So, by using specific surgical techniques to reduce bacteria, I can reduce the risk of ALCL to my textured implant patients, as Dr. Adams had mentioned.

We agree, it is critical to have innovative methods to facilitate better and more complete ongoing data collection of each type of breast implant for the lifetime of that implant. Our discussion and decision making with our patients should always be based on good data-driven science and a complete consent process, which is critically important.

I want you to know, from the Aesthetic Society, that we are listening to you, to Ms. Cook, to the women of the world, to the FDA, and we hear you. We are working tirelessly to understand more and provide more information and promote research into all issues related to breast implants. We are committed to providing the highest level of patient safety, but also sharing this information with our patients and the public in a timely and unbiased manner.

Thank you for listening.

DR. LEWIS: Thank you.

Dr. Laurie Casas.

DR. CASAS: I got a letter to speak tomorrow in the p.m. session, so I'm not sure why I'm listed in this session.

DR. LEWIS: All right. If you don't wish to speak, then --

DR. CASAS: I'd like to speak, but I wasn't prepared to speak today.

DR. LEWIS: Fine.

DR. CASAS: Can I speak tomorrow?

DR. LEWIS: Thank you.

DR. CASAS: Thank you.

DR. LEWIS: Ms. Jennifer Cook.

MS. JENNIFER COOK: Hello, my name is Jennifer Cook, and I'm from Georgia, and here is a photo of me, my husband, and 4-year-old son on vacation days before my diagnosis of BIA-ALCL in 2017.

As most of you know, the reports linking ALCL and breast implants began in the 1990s. In 2008 *JAMA* published an article recognizing that link. In 2010 a panel of experts looked at this long history and documented their agreement that the established scientific evidence is that a positive association does exist between breast implants and developing ALCL.

But sadly, in the latter half of that same year, my plastic surgeon and the manufacturer communicated to me the exact opposite. Here is what my consent form said: "There is presently no established scientific evidence that links either silicone or saline breast implants with cancer." I was given that informed consent because I was part of a study for an implant that was not yet FDA approved. Because I wasn't followed because I had a revision surgery shortly thereafter, I have concerns that my complications were never documented.

Years went by after my surgery, and don't you think my surgeon, or the implant manufacturer, should've made sure that I was directly aware that there was established evidence linking implants to cancer? But, instead, I remained in the dark. And do you know how I eventually learned the truth? I learned it randomly from middle school students in an inner-city school where I taught. The middle school students had written a play that made reference to media reports of implants causing cancer. Of course, I was shocked because I had been told just the opposite, and so I thought I was going to need to reprimand the students for making false, reckless statements.

But before I did that, I Googled it, and that's when I learned the horrifying truth. I read a lot about the BIA-ALCL, and shortly thereafter, I started to recognize that I actually

did have symptoms of the disease, and I went to the doctor. Even though I was informed, none of the doctors that I saw were, including radiologists and breast surgeons, and so I was unable to recognize and get a diagnosis until actually a year later, and by that time I had developed masses around my implant and, as a result, I had to have targeted chemotherapy as well as surgery.

I was blindsided. I was deceived. I don't want anyone else to go through what I am having to go through. One way to stop it is with mandatory standardized informed consent. Patients should not have to rely on their plastic surgeon, who may fail to stay up to date or may want to actually hide the facts.

In recognition of the FDA's desire for the patient perspective, I sent a document to Mr. Garcia suggesting what I think should be in part of a standardized informed consent on BIA-ALCL. Everything in that document I believe to be true, and patients have the right to know it.

Thank you.

(Applause.)

DR. LEWIS: Thank you for your comments.

Ms. Jamee Cook.

UNIDENTIFIED SPEAKER: Yeah, I think she's --

DR. LEWIS: All right, we'll move to the next.

Ms. Dawn Criss.

MS. CRISS: Good morning, my name is Dawn Criss and --

DR. LEWIS: Turn your microphone on, please.

MS. CRISS: Oh, I'm sorry. Good morning, my name is Dawn Criss, and I am from Alberta, Canada, and I have traveled here at my own expense.

I received my textured Allergan implants in 2008 when I was 38 years old, and I was

not warned of cancer or any type of disease. For 6 years I was healthy and working. Then in 2014 I experienced intestinal issues, chronic fatigue, unexplained rashes, itching, and massive hair loss. After months of suffering, my body shut down, and I was hospitalized for blood loss and severe ulcerative colitis and autoimmune disease. In 2017 my left breast swelled up twice its size. My physician referred me for an ultrasound-guided needle aspiration to test for lymphoma and an MRI to look for rupture. Both results were negative.

Despite my negative tests, I decided to remove my textured implants and replace them with smooth. In December of 2017 I had my first explant surgery, and it was determined that I had double capsules. The left inside capsule and implant surface tested positive for BIA-ALCL. Five weeks later I had a second surgery to remove the outside capsules and the new implants. Since my explant last January, all of my autoimmune symptoms have subsided. In the last year I have had only one major flare-up in which it took mere weeks to recover instead of months.

New patients need to know the risks of breast implants. The directions for use are given to plastic surgeons, and it lists numerous concerns such as autoimmune issues, gel movement without rupture, and depression. This information is given to plastic surgeons but not to the patient. Therefore, the patient cannot make a well-informed decision. Transparent informed consent with a two-page surgeon-patient checklist and a black box warning should be a priority for all new patients.

Please understand that not all women have obvious symptoms of this cancer, and some of them don't know about the disease until it is too late. False negatives from fluid collection is a common occurrence that cannot be ignored and testing the capsular tissue after explant can no longer be the only acceptable way to diagnosis. The long-term safety of all breast implants needs to be investigated. This should include BIA-ALCL as well as the autoimmune symptoms typical of breast implant illness.

While all breast implants can cause an immune response, textured have now been proven to cause this manmade cancer. Please take textured implants off the market. Continue studies through unbiased organizations, obtain accurate data from our current patient population, and include finding a more accurate way for testing and diagnosis that does not leave a patient at risk. We need to be able to work together within our healthcare systems to make sure that no one is denied testing or treatment because of their financial status, regardless if breast implants were an elective choice or not.

Cancer is a hard reality for many of us to deal with. It affects not only our bodies but our minds, our relationships, our working ability, and our own sense of security. For even the strongest believers it takes away hope. Cancer was not a choice, and we sure as heck didn't elect to get it.

Thank you.

(Applause.)

DR. LEWIS: Thank you.

Ms. Nicole Daruda.

MS. DARUDA: Thank you for the opportunity to speak. My name is Nicole Daruda. In 2005 I got Mentor's silicone cohesive gel breast implants. I was perfectly healthy before breast implants, and in the first couple years with implants, very marked symptoms appeared, and by 5 years, my declining health was so bad I had to leave my 25-year career. I'm not going to list all the symptoms because you're going to hear from many women about their systemic symptoms and our stories are mostly identical. Suffice it to say, I had serious autoimmune symptoms and diseases, endocrine gland damage, and kidney damage. I, along with multitudes of other women, feel duped into believing breast implants are safe, by plastic surgeons and manufacturers of implants.

After experiencing breast implant illness and researching, I found that silicone is not

safe or biologically inert, as described by my plastic surgeon, but rather it is made of an array of toxic chemicals and heavy metals that leak from early on and interact with our body glands, organs, and immune system, causing profound illness.

After experiencing this illness first hand, I realized that four generations of women and their families have been harmed over several decades, and due to the current trend of breast implants, there would be many, many more sick women.

I felt a deep responsibility to do something, and so in February 2013 I published a website called healingbreastimplantillness.com. Quickly, this website turned into a forum which is now 70,000 because my hunch was correct: there are multitudes of women that are profoundly ill from their implants.

Several hundreds of women arrive each day to our forum with the same story of symptoms, the same loss of health. We have all been repeatedly told our breast implants were safe or are safe and our symptoms are not from our implants, by both plastic surgeons and by family doctors who are misinformed. All of this illness and suffering could have been avoided if we had just been properly informed about the toxic chemicals and heavy metals of silicone and their real-world effects in our body and how breast implants leak much earlier than anyone expects and documented in your own data.

I cannot emphasize this enough. The crux of the issue is proper informed consent about the real failure rates of breast implants, the real-world effects of toxic chemicals and heavy metals of silicone, and the real health consequences of these ingredients in our body as not occurring. If women knew up front of the toxic chemicals and heavy metals in silicone and the real failure rates, they would never buy breast implants and this issue would disappear. If doctors knew the truth, they would not be misdiagnosing their patients. Proper informed consent is the only moral, ethical, and commonsense solution to decades of profound harm to women.

FDA, stop the manufacturers from hiding the truth that should be available to anyone considering breast implants. It's no longer possible for you or anyone to minimize breast implant illness. We are not going away. These issues are not going away. Please do the right thing by enforcing proper informed consent in respect to saline and silicone breast implants.

Thank you.

DR. LEWIS: Thank you.

(Applause.)

DR. LEWIS: Ms. Holly Davis.

MS. DAVIS: Yes. Hello, my name is Holly Davis. Can you hear me? Everybody, can you hear me? I'm often told --

DR. LEWIS: Move a little closer to the microphone, please.

MS. DAVIS: Closer.

DR. LEWIS: Thank you, that's excellent.

MS. DAVIS: All right, here we go. My name is Holly Davis. I'm from Charleston, South Carolina. I'm taking time from my work to be here for this momentous opportunity to stand here before this Panel. Thank you very much for allowing this, especially as it regards breast implant illness. And I have not been paid to be here to speak today. I'm speaking to best practices for informed consent discussions between patients and clinicians. I believe it's been stated over and over here today that we do not feel that we have been effectively and appropriately informed, that consent does not exist. The pamphlets that some manufacturers are giving to the plastic surgeons aren't making it to us. We are told very briefly about the inherent risks to surgery, not to the implants.

Let me just tell you first, please, my ladies here with BIA-ALCL diagnosed, stand again, please. Some of you may be in line. I cannot have this not be seen by the

manufacturers. Your numbers aren't equal to the people that are here today. How rare can this be?

(Applause.)

MS. DAVIS: This is North America. This isn't the world right now. Ladies that are suffering from BIA, BII, or any ASIA, anything else, please stand. Don't ignore us. We are real, okay? I got implants in 2002. I had a prophylactic mastectomy. Ladies, if you want to sit, go ahead, but I actually think that it kind of is helping for them to see you continue to stand here. There are people here today that want to tell us that implants are awesome.

I had a double mastectomy prophylactically. They found cancer in my left breast. I knew that it was a matter of when, not if. Damn it if they didn't find it in the left breast at the time I had my surgery. My surgeon I trusted, my team I trusted, Medical University of South Carolina. I was told in 2002 that they had the Mentor high-profile cohesive gel as part of a trial. Whoopee, lucky me, I could be in a trial and I get these, they're going to be awesome. And you know what, before my expanders were even -- they were finished with it, I had capsular contracture so hard I was paralyzed in my right arm, I couldn't move my head and my breathing was so compromised that I had to have surgery immediately to remove it. There was no talk about, gee, we should try something else. Instead, the implant was put in. Symptom after symptom came after that. I thought I was aging badly.

My memory became so concerning to me that I actually sought our neurologists at the Medical University of South Carolina. I asked specifically to start undergoing testing for Alzheimer's. I was told in the end that it was stress. Gee whiz, who suffers stress? I had two young children. Part of the reason that I had the prophylactic mastectomy, that I ended up feeling I cheated cancer. I can tell you right now, if I was told, and it has been said that is widely accepted that BIA-ALCL is -- it can happen. It's widely accepted. The manufacturers said it here today. Oh, but it's rare. I can tell you right now, and ladies that

are here, if you were told that you could have this, would you have gotten implants?

(A response of no.)

MS. DAVIS: Thank you. They would not have gotten implants, and of the ladies that are here that are happy with their implants, please, God let you stay safe. Okay, I wasn't safe. I explanted and I continue to have difficulties. Thankfully, my memory is coming back. It astounds my husband; he's very scared sometimes at what I can recall.

(Laughter.)

MS. DAVIS: I will continue to get better, and I will continue to support women, but I do believe informed consent has to be very clear. The black box. We need a checklist. We need to know what we're signing up for. It can't be a surprise down the road.

Thank you very much.

DR. LEWIS: Thank you.

(Applause.)

DR. LEWIS: Ms. Chandra DeAlessandro.

UNIDENTIFIED SPEAKER: She's not here.

DR. LEWIS: Dr. Lara Devgan.

DR. NOWILLO: Good morning. My name is Dr. Karoline Nowillo. I'm a board-certified plastic surgeon in New York. I'm here to present --

DR. LEWIS: Can you move closer to the microphone, please?

DR. NOWILLO: Can you hear me now? Good morning, my name is Dr. Karoline Nowillo. I'm a board-certified plastic surgeon in New York. My colleague, Dr. Lara Devgan, cannot be here today. I am here to read her testimony.

"My name is Dr. Lara Devgan. I am a woman who cares about breast health. I am testifying today as a board-certified plastic surgeon, the mother of six young children, and Chief Medical Officer of RealSelf. RealSelf is the world's leading online destination for

women interested in breast implants where nearly 100 million people a year go to learn about plastic surgery procedures and candidly review their experiences.

"Over 10 million people in the world have breast implants. Three hundred thousand women get breast implants every year in the United States, and about 1 in 20 adult American women have breast implants. In 2018 alone, people visited RealSelf 10,969,011 times to research breast implants. Through RealSelf, we have a tremendous amount of data to support the safety and efficacy of breast implants. On a population level, women are very happy and satisfied with their breast implants. Over 55,000 women have reviewed breast implants on RealSelf with nearly 97% of them saying that they are worth it.

"What we do is medicine, not magic. And life does not promise us perfection. However, this data echoes my experience in my medical practice where I have personally placed hundreds of breast implants for cosmetic reasons and cancer reconstruction in New York City. Placement of breast implants is a real medical procedure, meaning it has risks, benefits, alternatives, and indications, just like all medical procedures. Further, science is always evolving and maturing, and the more data that we collect, the more we can understand and improve our processes over time.

"Over 84,000 questions about breast implants have been asked on RealSelf, with more than 619,000 answers by board-certified plastic surgeons.

"I want the FDA to know that we care about our patients and we are committed to helping them.

"My message to those considering breast implants is that we, as board-certified plastic surgeons, are extremely committed to patient safety, information gathering, and the well-being of the people who put their bodies and lives in our hands. While I cannot predict the future, I can confidently say I would feel comfortable having breast implants myself or recommending them to my loved ones who desire them."

Thank you.

DR. LEWIS: Thank you.

Ms. Terri Diaz.

MS. DIAZ: Hi, my name is Terri Diaz. I am a breast implant illness survivor. Thank you for the chance to tell my story.

At 38 years old I was living the best life. I had a thriving business, I was in shape, I ate right, and I felt and looked my best. The only thing missing were the breasts I had before nursing my three beautiful boys. So, in 2006 I opted to have breast implants placed. My plastic surgeon chose Mentor high-profile saline implants. He told me that the implants were completely safe and that they were lifetime devices. He emphasized that they were the safe saline implants, and the only real complication would be rupture if I was to have a high-impact injury to my chest.

Within months of implant surgery, I started having symptoms such as migraines and unexplained weight gain despite my healthy lifestyle. I started then having flu-like symptoms that I could not relieve. The symptoms kept accumulating. I was referred to countless doctors of various specialties. By the 6-year post-implant, I was diagnosed with multiple autoimmune illnesses. I was completely bedridden, waiting to die. I couldn't even walk up a flight of stairs. Not one of the medical professionals that examined me considered my implants as the cause of my illnesses. Luckily, my life-long friend, a science researcher, suggested that it could be my implants. I started researching and found a website and Facebook group that had at the time 3,000 members, all who had some variation of my symptoms. It was from these women, not one of the medical -- sorry. It was from these women, not the doctors, not the manufacturers or the FDA, that I was educated on this disease and how to properly do explant surgery.

From seeing the desperation of women looking for answers for their illnesses, I

decided to facilitate a local illness group. That was almost 3 years ago. My group, Breast Implant Illness Florida Support Group, grows by the hundreds every month. Not only am I telling my story, but I'm here representing them. I am inboxed daily by hopeless women, many who've lost thriving careers with no finances and unable to afford healthcare. This health crisis affects all of us and has been going on for decades. The other multiple groups on social media that I'm involved with, they grow by the hundreds daily, totaling nearly 150,000 women.

Breast implant illness has cost me everything. I had to close my thriving business. I'm in the process of being accepted into a Chapter 13 and home loan modification, but I still may lose my home. I can no longer afford health insurance and cannot afford medical care.

Today, I am no longer bedridden, and I'm about 85% better. The only medical procedure I had was the explantation of my implants. I lost 10 years of my life due to safe implants. My symptoms are up there. Those are the ones that are gone since I've explanted.

My plea to you is this: informed consent; provide a black box warning on all breast implants, mandatory; patient information booklet; doctor-patient checklist; chemical data transparency; and mandatory testing for BIA-ALCL for all women explanting.

I appreciate your time. I know you are hearing us. Thank you.

DR. LEWIS: Thank you.

(Applause.)

DR. LEWIS: Dr. Gloria Duda.

DR. DUDA: Good morning, my name is Gloria Duda, and I am a board-certified plastic surgeon and a member of the Aesthetic Society. I've been in private practice in McLean, Virginia, since 1992, and I have no conflicts of interest and no financial interest in

industry. I spoke during the General and Plastic Surgery Devices advisory meeting in 2015 and 2011, and I appreciate the opportunity to speak again today, now regarding my last 27 years' experience with over 6,000 patients who have received silicone breast implants either for cosmetic reasons or for breast reconstruction.

Over the past 27 years, thousands of women have returned for follow-up visits and expressed their satisfaction with their breast implants. During consultation, I have a transparent dialogue with my patients reviewing the benefits and the risks regarding their procedures. My patients stated that breast implants have made a positive impact in their lives, either restoring confidence and self-esteem or a sense of normalcy after mastectomy. When asked if they would make the same decision again, the overwhelming response has been yes.

Patients have returned to my practice for secondary breast procedures regarding capsular contracture, implant rupture, or cosmetic changes due to the aging changes of the breasts. In discussing their surgical options, removal of their implants without replacement is discussed, and 90% of our patients have elected to have their implants replanted. None of my previous 6,000 breast implant patients have returned requesting removal of asymptomatic breast implants, and none of my patients have complained of breast implant illness. I have seen new patients requesting removal of their implants for various reasons, including undiagnosed systemic symptoms. We counsel them that their implants can be removed; however, their symptoms may not be related to their breast implants. I do have one patient who was diagnosed with breast implant-associated anaplastic large cell lymphoma 5 years after her textured implant was placed. She was appropriately treated, and she remains free of disease now, 3 years later.

Like many, my patients have not been compliant with the MRI follow-ups for detection of asymptomatic rupture, and the reasons that they include are the expense of

the MRI, radiation exposure, false positive readings that lead to unnecessary surgeries, and there remains a need for a less invasive in-office procedure to assess the implant integrity.

As plastic surgeons, we are patient advocates. We're committed to our patients with respect to education, safety, and satisfaction. Patients have easy access to information through the media; however, this information is not always based on credible data and that can also be sensationalized. It will be beneficial for all of our patients if the media chose to also include positive information and the overwhelming satisfaction regarding breast implants. Until objective data is collected on breast implant illness and breast implant-associated anaplastic large cell lymphoma and definitive decisions can be made, I'm here to advocate the continuation of a woman's right to have an informed choice regarding her breast implants.

Thank you. I'm appreciative of the opportunity to be part of this important assessment. Thank you.

DR. LEWIS: Thank you.

Dr. Claire Duggal.

DR. DUGGAL: Good morning, my name is Claire Duggal, and I am a board-certified plastic surgeon in private practice. My practice is focused on breast surgery, and I place breast implants for both cosmetic and reconstructive purposes. With access to all of the information and studies currently published relating to breast implant safety, I choose to place all available types of implants, including saline, smooth silicone gel, and a limited number of textured silicone gel implants. I personally have textured implants placed for cosmetic reasons, and I can attest firsthand to the immense benefit breast implants can have on body image and quality of life for many women.

I have not personally taken care of any patients with BIA-ALCL. I do discuss the growing body of evidence related to this condition with every patient. It is definitely a

factor when deciding which type of implant to place for each individual patient. If a patient has an anatomic or technical reason why a textured implant might be a better choice for them, including a history of implant malposition, a history of capsular contracture, the desire to have implants placed on top of the muscle or the desire to have an anatomically shaped implant, I have a long discussion regarding the risk of ALCL, the signs and symptoms and the treatment plan. I explain to patients that implants are intended to make them feel more comfortable with their body, not create additional anxiety, and together, we make the decision if a textured device is appropriate for them.

I also occasionally see patients with a varied constellation of symptoms which are referred to as breast implant illness. These women most often have no palpable scar tissue, no evidence of implant rupture, no lab abnormality, and a thin filmy capsule which can be difficult, if not impossible, to completely remove, making the diagnosis difficult and frustrating for all involved. By the time I see these patients, they have generally decided their implants are the problem and desire removal, and I do not ever hesitate to remove implants for anyone that would like them out. I have found that some patients experience an improvement in their symptoms after implant removal and some do not, and we discuss this prior to explantation.

I practice longitudinal care and offer lifetime evaluations to my breast implant patients. The overwhelming majority are happy with their implants and experience improved quality of life after surgery. I feel responsible, as a surgeon, for having the most up-to-date information about implant safety in order to be able to appropriately counsel patients, and I believe that the preoperative discussion with patients is of paramount importance in helping them to make an informed decision regarding their bodies.

Thank you very much.

DR. LEWIS: Thank you.

Ms. Julie Elliott.

MS. ELLIOTT: Good morning. Ladies and gentlemen of the Panel, please bear with me as my first language is French. My name is Julie Elliott, and I'm from Quebec, Canada. I have Mentor smooth cohesive gel implants for 10 years. When I decided to get breast implants, I knew every surgery has its risks and that implants could rupture or cause contracture. But my surgeon said that the newest generation of implants were impossible to rupture, and the cohesive gel would never leak. Implants transformed me from an athlete with a full-time job to a full-time patient.

Three weeks after getting my implants, I noticed the first changes in my health. I experienced extreme exhaustion, rapid weight gain, paralyzing brain fog, intolerance to sun and heat. Nine months after getting my implants I was diagnosed with Hashimoto disease. Later on, I experienced muscle pain so severe I had to stop exercising. My hair was falling out, and I was always thirsty. I was also diagnosed with asthma. I then developed food allergies, my throat was closing after each bite, and my gastrointestinal issues became so severe that I had to stop working.

In 2016 I read about breast implant illness. I had been searching for the cause of my health problems for 10 years, and it was right in front of me. I have two polymer bags inside of me. I had my implants removed in January 2018. A month after my surgery I sent my implants and capsule to be analyzed by Dr. Pierre Blais in Ottawa. My capsules were a hundred times thicker than what he usually sees and were covered with granulomas. But the most shocking was the fact that one of my implants had a micro-rupture of longstanding origin that had leaked silicone oil into my body for years. After my explant surgery, several of my long-term symptoms disappeared almost immediately. Today marks my 14 months since my implant surgery. While some of my symptoms still remain, I am healthier than I've been in years. My implants greatly compromised my health, and it may take years, it may

take years to recover.

I decided to create the first French Canadian support group for women affected with breast implants. The group immediately got to over 800 members and growing every day, and these members are actually 800 patients. I stand in front of you because women are literally dying from their implants and no one believes them. We need more long-term research studies on the complications from breast implants that focus on symptoms and not just diagnosis.

I stand in front of you because I see women fighting every day to get proper testing for BIA-ALCL. Healthcare providers need awareness on the latest developments about diagnosis, pathology, and treatments for this cancer.

I stand in front of you because every day I see women who have no clue what kind of implants they have inside their bodies. We need national registries that tracks all complications and not just reoperations.

I stand before you because I know the FDA can lead the way and be the role model we need. This meeting is FDA's opportunity to listen to what patients are saying about their experiences with implants so that public health agencies make decisions that will help shape the future health of millions of women around the globe.

Thank you for this opportunity.

DR. LEWIS: Thank you very much.

(Applause.)

DR. LEWIS: Ms. Terri McGregor.

MS. McGREGOR: Good morning, my name is Terri McGregor. I traveled from Ontario, Canada, at my own expense.

Four years ago, I was diagnosed with ALCL from breast implants that were 6 years old. My diagnosis was Stage IV. The joy of life was cut short by a profit-driven manmade

cancer. Life as I knew it ceased to exist. Clinic appointments, tests, exams, chemotherapy, debilitating side effects, and excruciating procedures drained my reserves. I failed six rounds of CHOP, I failed relapse chemotherapy, and my prognosis changed to terminal with 4 to 6 months to live.

I received rituximab under clinical trial through our national healthcare system in Canada, and after four rounds I was NED, no evidence of disease. I underwent a stem cell transplant as my best hope for long-term survival. I have recently been given my second cancer diagnosis, a complication from transplant.

Being a vanguard in round two for a club I never wanted to join is unbelievable. Our patients are facing reoccurrence and complications from this cancer. I have never been asked to participate in a study for BIA-ALCL. In my deepest thoughts and most private moments, I ask myself if I can endure a repeat of the excruciating effects of treatment.

Well, I did my best to put on a brave face as a mom, a wife, and a daughter. I watched my loved ones struggle as I became a typical cancer patient, and they were helpless. My health declined. The isolation, betrayal, loneliness of our cancer is compounded by the dismissive public relations campaign by industry. While patients and clinicians called out on the emerging evidence, the industry stayed silent. When our existence could no longer be denied, we were merely portrayed as an anomaly. Our disease status was to be reported to the FDA by the manufacturers who created our cancer. Allergan took 19 months to send a follow-up from my reporting physician. With FDA annual reporting, Allergan was able to avoid confirming my case for 3 years. Underreporting and undiagnosed are common and unacceptable. I collaborated with Dr. Peter Lennox at the CSBS in Canada to assist collecting our 28 Canadian cases. The five cases reported by the manufacturers to Health Canada did not include me.

Our advocacy team helps thousands of women every day with awareness and

education. We want clinicians to be the experts, not patients. The presence of an implant has become a detriment to oncology investigation. We patient advocates request a seat at the table. We ask surgeons to contact their past patients with or without FDA recommendation. Lastly, please vote your full authority to withdraw all textured implants and expanders from the market and end the suffering of tomorrow's families.

Thank you.

DR. LEWIS: Thank you.

(Applause.)

DR. LEWIS: Ms. Danielle Valoras.

MS. VALORAS: Hi, my name is Danielle Valoras. I'm a physician assistant, and I've worked in the medical device research industry for over 20 years. I love innovation. I'm also a BII survivor. Thus far, breast implants have cost me over 3 years of my life and over $100,000. FDA, I'm asking for you to hold the device manufacturers accountable to conduct the appropriate long-term safety studies and ask the appropriate questions.

Two: Initiate a patient checklist providing full disclosure on the surgical and biomedical risk of breast implants.

Three: A declaration from you, the FDA, recognizing that breast implant illness is real so those affected can get the support they need.

My breast augmentation was in December 2015. I was 48 years old, and I lost 40 pounds. I was in the best shape of my life, and I wanted to look as good as I felt. I met with my plastic surgeon, and he recommended breast augmentation, saying it would be a perfect fit for me and the only real risk would be that of anesthesia. There was no mention of the associated risks for those of us with a history of autoimmune disease.

Fast forward almost 2 years, I was in and out of hospitals and doctors' offices with migraines, swelling, muscle pain, fatigue, common symptoms that we BII people have. I

kept looking for answers, and I soon realized I needed to remove my implants. It took multiple visits and over a year before I can convince a plastic surgeon that the implants were a problem. When my lymph nodes started to swell, the doctor finally became concerned and agreed to explant. I became extremely ill, and surgery seemed unwise until I got better. I never got better, but I knew I needed to explant, so I did October 2017.

Immediately after the explant, the swelling, migraines, joint pain, were all gone. My inflammation markers and my heavy metal levels also went down. Please note, my implants did not rupture. There's a slide to go with my presentation, and it's not here. Is there -- there we go. And one more. This is a picture of me, and on the left you can see a thermography with implants and depicting the red and the yellow is inflammation. Two weeks post-explant, I wanted to see if the inflammation was still present, and you can see it is greatly diminished.

I have worked -- I was told that these could not cause any physiological issues, and obviously, that's not true. I've worked on many Class III clinical trials, and it is mind blowing that the FDA did not require better safety data and did not hold the companies accountable. When I look through the MAUDE evidence online, through February 2019, there have been over 51,000 adverse events. Over 43,000 were injury related, and 116 were death related regarding breast implants. There are lifesaving devices that are worth the risk of serious harm. Breast implants are not one of them. The FDA is a public health agency. The taxpayers should be your most important customers, not the device companies. Please require that the manufacturers boldly display potential risks for cancer and autoimmune issues and hold them accountable. We need more longitudinal studies on how to best treat implant victims, so they can regain their health. The first and most important step for the FDA is to acknowledge that breast implant illness is real, and until that happens, thousands more will be harmed.

Thank you.

(Applause.)

DR. LEWIS: Thank you.

Mr. Steven Teitelbaum. Not here?

(No response.)

DR. LEWIS: Dr. Mary Gingrass.

DR. GINGRASS: My name is Dr. Mary Gingrass. I'm a board-certified plastic surgeon, and I've been in practice for 24 years. The majority of my practice is cosmetic breast surgery. I also have silicone breast implants. And I have no disclosures. I'm here at my own expense.

My goal today is to inform the Panel that the FDA's current recommendations for MRI for detection of silent rupture have not turned out to be clinically practical. A recent study by the Aesthetic Society found that less than half of members routinely order MRI for routine surveillance. The reasons given were cost, compliance, high false positive and false negative results.

Clinical data and real-life experience show that doctors aren't ordering and patients aren't getting these MRIs. Most of the time, the MRIs are ordered when rupture is highly suspected or when it may change the operative plan. On behalf of the Aesthetic Society, myself, and most importantly my patients, I would like to suggest that high-resolution ultrasound, mammogram, and self-breast exam are more practical modalities for routine surveillance.

I would like to recommend that the FDA recognize ultrasound surveillance starting at 10 years after implantation and then every 5 years thereafter. This is based on data that rupture rates for the newer fifth generation implants do not exceed 10% until after 10 years.

This imaging demonstrates the ease of differentiating an intact implant on the left and a ruptured silicone implant on the right. This is a comfortable, fast procedure and can often be done right in a physician's office.

This sentinel publication published in 2012 demonstrated the efficacy of ultrasound in monitoring patients and identifying rupture. A more recent follow-up study by the same authors has evaluated 700 breast implant patients. Patients were assessed with ultrasound preoperatively, and then the results were confirmed intraoperatively. The sensitivity of the ultrasound was 98% and the specificity 100%.

The bottom line is that both doctors and patients need a more accessible method for surveillance. I propose that the FDA add high-resolution ultrasound, combined with routine mammogram and self-breast exam and, of course, physician follow-up as an accepted modality because it is more practical, less costly, and maybe even more effective than MRI.

Thank you for allowing me to speak.

DR. LEWIS: Thank you very much.

Dr. Foad Nahai.

DR. NAHAI: I'm Foad Nahai and I'm a board-certified practicing academic plastic surgeon and the current Editor-In-Chief for the *Aesthetic Surgery Journal*, *ASJ*, the flagship journal of the Aesthetic Society. The journal has the highest impact factor of any journal in its class, with circulation in the United States of approximately 4,000 and worldwide circulation of over 6,000. I have no financial disclosures.

The goal of the journal is to advance the science, art, and safe practice of aesthetic surgery and cosmetic medicine through the publication of peer-reviewed, data-driven, evidence-based clinical and research studies. The FDA has called the meeting to address the data on the risk-benefit of breast implants. As the world's premier aesthetic journal, we have published many peer-reviewed studies on the seven concerns of the FDA. In our

current March 2019 issue, we published a supplement on BIA-ALCL containing the latest, most accurate information on the etiology, diagnosis, and treatment of the condition. The aesthetic journal has also published peer-reviewed information on systemic symptoms reported by patients with implants and has published on and has encouraged the establishment of breast implant registries worldwide.

The aesthetic journal consistently publishes works on detection of silent implant rupture with MRI and, as we just saw, the alternative ultrasound technologies. We publish featured articles on the application of surgical mesh in breast surgery, best practices articles on breast implant surgery, as well as on informed consent, informed consent which always highlights the unique nature of this concern as new data and clinical findings surface.

Lastly, the *Aesthetic Surgery Journal* is a source of peer-reviewed patient-centric data following breast implant surgery. Our peer-review system is double blind and free from any conflict of interest. As editor, I have always maintained that the role of any scholarly publication is to publish opposing views and to encourage debate and discussion.

Ongoing data collection on breast implants is critical, and I assure you that *Aesthetic Surgery Journal* will continue to publish peer-reviewed, data-driven scientific manuscripts with the goal to further our collective understanding of the risks and benefits of breast implants which will continue to empower plastic surgeons and their patients with high-quality information to ensure all care decisions are based on the best available evidence.

Thank you for your time.

DR. LEWIS: Thank you.

(Applause.)

DR. LEWIS: That ends our public presentations, and I want to thank all of the speakers who presented their eloquent and very personal issues relative to breast implants. I believe that your comments and descriptions have been extraordinarily helpful to the

Panel in pointing to directions forward, and I thank you all for doing so.

We will now break for lunch. Panel members, please do not discuss the meeting topic during lunch either among yourselves or with the audience. We'll reconvene at exactly 1:10 and continue the afternoon session. Thank you.

(Whereupon, at 12:28 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:09 p.m.)

DR. LEWIS: I'd like to call the meeting back to order. People please take their seats. We're going to go off agenda for 5 minutes in order to allow Dr. Karen Nast of the FDA to reply to some questions raised by Dr. Li in the previous session.

MS. NAST: Thank you. I'm Karen Nast. Thank you for giving me a moment to respond to the questions, a few questions, I believe, from Dr. Li from the previous session.

So, as you see on the screen, these are all of the medical device reports we received by year. I hope that answers your question.

(Off microphone comment.)

MS. NAST: These are all medical device reports for silicone and saline breast implants. The next slide.

The earliest date of a BIA-ALCL event in the MDR database is from 1996. That was the date of the event. The earliest MDR reported to us of BIA-ALCL came in 2010. In 2011 we identified 17 total reports. In 2016 we identified 258 total reports. In 2017 we identified 359 total reports. In 2018 we identified 414 total reports. This year we identified 660 total reports with 457 unique reports. Next slide.

These are the tables from our website. This was from 2011. The next slide. This was from 2016, 2017, and 2018. These are cumulative reports and unique reports. I hope this has helped clarify your questions.

DR. LI: Yes, thank you very much. Just a quick question. Is there any way to identify whose implant these are? In other words, you know, you're going to -- you're breaking it down for us, for instance, silicone and saline, but I don't know whose they are, and a textured implant, I don't know whose they are. Is there a way to pull that out?

DR. ASHAR: Some of the reports provide that information, but many of them do not,

and so we used the information that we could obtain from the medical device reports regarding, you know, the characteristics of the device.

DR. LI: So, it's difficult, then, to --

DR. ASHAR: It is difficult, although manufacturers are required annually to report to us the number of cases that they're aware of, of BIA-ALCL.

DR. LI: And just one last little detail question. In a part of the Panel pack you listed the FDA-approved devices and some of these -- for instance, on a saline device, both a textured and a smooth was offered under saline. So, when you say silicone and saline here and textured and smooth, how do we break that down? In other words, when it says saline, that includes both textured and smooth, and when you say textured, it includes both saline and silicone?

DR. ASHAR: That is correct.

MS. NAST: Yes.

DR. LI: Thank you.

MS. NAST: Any other questions?

DR. LI: No, thank you very much. I appreciate it.

MS. NAST: Thank you so much.

DR. LEWIS: Thank you, Dr. Nast.

We'll now resume the regular agenda and proceed to a presentation regarding the U.S. National Breast Implant Registry, which will be presented by Dr. Andrea Pusic.

DR. PUSIC: Thank you and good afternoon. I appreciate the opportunity to speak to this Panel. I'm Dr. Andrea Pusic. I'm a board-certified plastic surgeon, Chief of Plastic and Reconstructive Surgery at Brigham and Women's Hospital in Boston and a Professor of Surgery at Harvard University. My clinical focus is breast reconstruction and the care of cancer patients. My disclosure is that I'm a co-developer of the BREAST-Q, which is a

patient-reported outcome measure, and I receive royalties when it's used in for-profit industry-sponsored clinical trials.

I'm currently the president of the Plastic Surgery Foundation, which is the charitable arm of the American Society of Plastic Surgeons. The ASPS is the largest plastic surgery specialty organization in the world with a membership of over 8,000 U.S. plastic surgeons. Approximately 93% of board-certified plastic surgeons are members of the American Society of Plastic Surgeons. The PSF supports research and education related to plastic surgery with the primary goal of ensuring patient safety, optimizing outcomes, and supporting innovation.

The PSF believes that clinical registries are powerful means to understand real-world outcomes and to monitor safety signals. We fully support the FDA's vision to establish a national evaluation system for medical devices which includes registries as a valuable source of real-world evidence.

Well-designed patient registries have and will continue to demonstrate their value for providing a vitally important view of clinical practice, patient outcomes, safety, and comparator effectiveness.

Since 2002 the Plastic Surgery Foundation has established five highly successful clinical registries under the banner of the Plastic Surgery Registries Network. As an example, the first registry that we established, TOPS, for Tracking Outcomes and Operations in Plastic Surgery, has collected clinical outcomes data on over 1.6 million plastic surgery procedures with a dedicated module for breast surgery and clinical information on approximately 200,000 breast implant procedures.

In the context of breast implants, national registries are particularly important because a majority of these devices are placed for cosmetic reasons in healthy women who may not be seen regularly by physicians. Furthermore, the period of time when the implant

is placed, and the development of adverse effects may be many years, further complicating efforts to collect accurate implant data. Standardized and valid registries are thus an essential means to prospectively detect poorly performing implants and/or the development of new complications over time, nationally and internationally.

In 2011, when concerns were initially being raised about a new type of lymphoma associated with breast implants, the PSF recognized the need to establish a national registry of BIA-ALCL cases to allow for a better understanding of the etiology, natural history, causation, and optimal treatment. At that time, the PSF entered into a cooperative research and development agreement with the FDA, a CRADA, to establish this new registry called PROFILE. For the first 3 years after PROFILE was established, I was the PI of this registry, and since 2014 it's been led by Dr. Colleen McCarthy, who will be speaking to you tomorrow.

PROFILE is a clinical rare disease registry that collects essential information on patient characteristics, disease presentation, diagnosis, pathology, treatment, clinical course, and the outcomes of BIA-ALCL. PROFILE enhances our true understanding of ALCL because it systematically collects detailed information that is not gathered in MAUDE or during the MDR process. Given the often complex nature of these cases, information submitted to PROFILE is completed by physicians to ensure high data quality. When patients reach out directly to PROFILE, our team facilitates having their surgeon participate on their behalf.

Since its establishment, PROFILE has received information on 267 cases of BIA-ALCL in the U.S. We have a team of clinicians and registry staff that review and verify all case information to seek complete case capture as well as to ensure there are no duplicates. One challenge that we have faced, however, is it's often difficult to obtain this information from large academic institutions because of concerns about privacy and data security. We

would thus ask the Agency to continue to work with the Plastic Surgery Foundation to ensure that large academic institutions, healthcare systems, and physicians are motivated and/or are required to participate in PROFILE.

The PROFILE registry experience has led to a number of very important clinical insights which were published recently in the *Journal of Plastic and Reconstructive Surgery*. This is the first published manuscript from PROFILE, and others will be written and added to the scientific literature as new data is accumulated and analyzed. This March 2019 paper highlights many important findings about the clinical presentation from this large cohort. Specifically, we note that the average time from breast implant placement to a development of ALCL was 11 years, pointing to the importance of long-term implant surveillance. All patients in the registry had a history of exposure to a textured device, and 86% of cases presented with a seroma.

Through this first publication and offered through regular communication with our member surgeons across multiple media, we're informing surgeons about the importance of timely and thorough assessment of new seromas and best practices for optimal treatment if ALCL is diagnosed. Dr. McCarthy will be presenting more on this tomorrow.

The PSF experience working with the FDA to develop PROFILE helped us to appreciate the opportunity and the need to establish a national infrastructure for breast implant surveillance in the United States. To that end, the National Breast Implant Registry was developed, or the NBIR, as a multi-stakeholder initiative that included surgeons, patient advocates, epidemiologists, the FDA, and breast implant manufacturers. Along with Dr. Charles Verheyden, I'm co-PI of the NBIR which was launched in October 2018.

Our goal was to create a structured national registry to be inclusive of all breast implant patients, culling best practices and registry design. While the NBIR is part of the PSF Plastic Surgery Registry Network, all surgeons, irrespective of whether they are ASPS

members or whether or not they are plastic surgeons, are able to contribute.

The NBIR will provide real-world data that can be used to track how patients respond to their implants and how the implants perform over time. It has several key features designed to ensure high data quality. Firstly, it has an opt-out design to minimize inclusion bias and to ensure the highest volume of case collection.

Secondly, it collects structured validated data elements using internationally agreed upon data definitions. I'll talk more about ICOBRA, which is the International Collaboration of Breast Registry Activities, in a moment. But since its inception, the PSF has been actively involved with ICOBRA to ensure that the NBIR is collecting the same data elements in the same way as other large international registries. The potential for comparison across multiple large international registries is very important, as is the potential for data linkage with other national registries in the United States. The NBIR is part of the FDA's Coordinated Registries Network, and together, we've been exploring novel and powerful ways to link clinical variables and patient outcomes across registries in the area of women's health.

The NBIR was also designed to have sub-studies related to specific questions and concerns within a larger cohort. Nesting studies within the NBIR will allow us to study specific issues in depth, while maintaining the breadth of data collection across the entire registry. This design also supports the possibility of embedded post-approval studies within the NBIR to collect real-world evidence, facilitating the safe introduction of innovative implants into the United States.

And, finally, the NBIR offers electronic capture of unique device identification data, or UDI, using a barcode scanning app which links to the FDA's GUDID database to provide up-to-date, accurate device information while reducing the risk of data entry error. This technology and the FDA's willingness to support its integration can lead to more accurate

and complete information on implanted devices.

Patient and device data are entered into the National Breast Implant Registry at the time of implant placement and/or reoperation. Importantly, the NBIR was designed to leverage device tracking regulation which aligns with these clinical events. Device tracking is a federally mandated requirement of manufacturers of silicone implants, wherein patient and device information is collected at the time of implant placement and removal and sent to the companies, so in the event of a recall or safety issues patients can be contacted. This process is currently performed by pen and paper and scanning of forms. When the NBIR was designed, we worked with the implant manufacturers to ensure that device tracking elements were included in our case report form. This means that surgeons participating in the National Breast Implant Registry can simultaneously fulfill the device tracking requirements.

I'm very pleased to say that as of July 1, device tracking data collected in the NBIR will be sent to the manufacturers in accordance with federal requirements. Through this mechanism, we will increase registry participation among our surgeons, minimize duplicate data entry in the operating room, and also likely improve the quality of device tracking data submitted.

When I worked to establish the National Breast Implant Registry, we've been greatly encouraged by the positive experience of breast implant registries internationally. As I mentioned, ICOBRA is the International Collaboration of Breast Registry Activities and The PSF was among the founding members. There are now 15 countries in this collaboration.

As an example of how successful a registry can be, I'd like to highlight the experience of a Dutch national registry which was initiated in 2014. Like the NBIR, the Dutch registry is a national prospective opt-out registry. Mandatory registration of all plastic surgeons in the Netherlands was instituted in 2016. This registry now has data on the experience of over

26,000 patients.

Just as significant as the total number of patients in the registry is the fact that nearly 90% of all eligible Dutch surgeons are participating. This is particularly important in light of the fact that a woman who has a complication after breast implant surgery may not return to the same surgeon who put the device in initially. She may see someone else. To accurately quantify the risk of complications and reoperation, we do need to encourage all surgeons to participate in our registry. As we now incorporate federally mandated device tracking into the NBIR, I think we have the potential to achieve this, as has occurred in the Netherlands.

The Plastic Surgery Foundation very much appreciates the importance of the patient's perspective, the patient voice. We understand that there are things that only patients can know and tell us about if we ask. Over the past decade, we've worked hard to advance the science of patient-reported outcome measurement. We've convened two conferences on this topic, one sponsored by AHRQ and one by PCORI, and we have developed and validated a number of plastic surgery specific patient-reported outcome measures, or PROMs. PROMs are questionnaires that allow us to accurately and precisely measure symptoms like pain and outcomes like patient satisfaction with their breasts. Through this research, we've been able to quantify some of the important benefits that breast implants can provide in terms of quality of life and body image. Equally, we've been able to better appreciate some of the adverse effects such as how capsular contracture can cause pain or decrease physical function.

When we built the National Breast Implant Registry, it was always with a view to incorporate patient-reported symptoms and outcomes into the registry. Why is this so important? Because we know that reoperation or device removal is a relatively late indicator of a problem. PROs are just that much more sensitive. Also, in the context of

cosmetic breast augmentation, we know that women may suffer with a problem for years but not seek medical attention because of the cost involved. Assessing PROs can best give us a much more accurate appreciation of adverse effects. This is particularly important to consider as we develop our strategy to better understand reports of breast implant illness. Using a national registry to evaluate, benchmark, and monitor symptoms among women with breast implants would be a very powerful way to investigate some of the concerns that we're discussing today.

I'd like to share with you another example of a very successful international registry and specifically one that collects patient-reported outcomes. The Australian National Breast Implant Registry was established in 2012 and, like the Dutch registry, has grown very significantly since then. There were just over 25,000 patients in 2017, and now there are 38,000 patients in this registry.

Because of the PSF's experience in PRO measurement, the leadership of the Australian registry asked us to help them design and conduct a pilot study of patient-reported outcomes within their registry. Essentially, the goal was to establish feasibility and an optimal approach to patient engagement. And online, this experience would also guide future efforts to incorporate symptom assessment and PROs into the National Breast Implant Registry. And so, with our Australian colleagues, we developed and tested five questions, two of which were related to symptoms, pain, and tightness, and three related to appearance and breast feeling. These questions were then administered to patients either through text message or email at 1 year, 2 years, 5 years, and 10 years after surgery. This experience was very successful, and in the pilot phase the response rate was 76%. Since the completion of the pilot, the Australian registry has gone on to collect over 5,000 cosmetic augmentation patients' data and close to a thousand reconstruction patients.

In 2019 we will begin to incorporate assessment of patient symptoms and outcomes

into the National Breast Implant Registry in a similar fashion to the Australian registry. As I said, incorporation of PROs in the MDR is particularly important in the context of breast implant illness.

I envision incorporation of PROs into the MDR that will happen perhaps in two ways, one broad and one deep. The first would follow the Australian experience, wherein we would invite all women to answer a very limited number of questions on a regular basis, perhaps annually, and we will follow these patients for a long period of time, ideally well beyond 10 years. This data collection would be primarily aimed at identifying safety signals related to poor implant performance or any new or emerging issues. We also plan to collect more comprehensive PRO data in a cohort of patients nested within the registry. This would be a more in-depth prospective assessment of systemic symptoms designed to inform our understanding of BII and autoimmune-related concerns.

In conclusion, the ASPS and PSF consider patient safety to be paramount. We also believe that discussions about breast implant safety should be based on strong scientific evidence and high-quality data. This is the only way we can accurately inform women, surgeons, and regulators in a balanced and constructive way. The National Breast Implant Registry is central to this effort. It collects high-quality, structured data using internationally agreed upon data definitions and core elements.

We also fully appreciate that the assessment of patient-reported symptoms and outcomes can be an even more sensitive indicator of safety signals than surgery. As planned in 2019, we'll thus begin piloting the collection of PRO data in the NBIR patient population.

With incorporation of patient-reported outcomes, linkage to other U.S. registries through the FDA's Coordinated Registries Network, collaboration with other breast implant registries internationally, and nesting of sub-studies within the registry architecture, the

NBIR can inform our understanding of breast implant illness and also provide important safety signal data should new concerns arise in the future.

Given the pressing and persistent safety concerns around breast implant surgery, the PSF believes that participation in the National Breast Implant Registry should be considered a key component of high-quality care. We would thus welcome any recommendations that the Panel might make to encourage broad adoption of registry participation as has occurred in other countries.

Thank you.

DR. LEWIS: Thank you very much.

We'll now proceed to a presentation from the MD Anderson Cancer Center on BIA-ALCL by Dr. Mark Clemens.

DR. CLEMENS: Thank you. Thank you to the Panel for the invitation to present to you today. I have the following disclosures. I recruited patients for Mentor and Establishment Labs' clinical trials and was an Allergan consultant from 2012 to 2015. I serve in a number of roles that are pertinent to my role today, specifically a lymphoma author for NCCN guidelines, but I would say, first and foremost, my primary responsibility is to my patients whose trust in their safety they give me.

We've treated 64 cases of breast implant ALCL at MD Anderson, and up on the screen I've placed the FDA 2019 numbers in the middle, with the PROFILE numbers to one side and the MD Anderson tracking for the United States on the other, and we can see the average time to development of the disease is 8 to 10 years. And we recognize unique and confirmed cases, 152 in the United States, and the shortest time interval to the development of the disease from the implant is 2.2 years.

We can see the most common presenting symptom is delayed seroma; however, capsular contracture, mass, as well as an overlying skin rash have been described. There is

no testing or screening for asymptomatic patients.

If we do look, we do see smooth has been reported in both PROFILE and FDA, but it's important to note that no smooth-only implant cases have been reported in any case report or case series to date. There is an even mix of cosmetic and augmentation, an even mix of silicone and saline, as was augmentation and reconstruction.

And I want to harp on -- if you take one thing from my presentation, it's this idea of smooth. There is no pure smooth cases to date. If we look on the FDA website, which had 30, it's important to note that they either had a mixed clinical history or no clinical history available for review. You'll see in your packets that you received from the FDA that it says if there's case reports, there's no citation or reference on that line that there's case reports.

So, there is misidentified three manuscripts in the literature, one by Adams 2015, one by Largent 2012, one by Lazzeri 2011, which are commonly miswritten as smooth implant cases. I've included the pertinent paragraphs from the manuscripts, showing that they are actually unknown device history, not smooth implant history. There is no smooth implant case, not in any series, not any case report, not any case registry.

There is, however, cases related to other implants, so tibial implant; one patient developing CD30 positive, ALK negative around four different dental implants; a gastric lap band, a shoulder repair, a chest mediport. However, this is it; this is all of them. I will add two gluteal implants. You're right that the one out of USC was not diagnosed around the implant, but the second one out of Sao Paulo was diagnosed in periprosthetic fluid. That case was actually a textured breast implant placed into the gluteal pocket, interestingly enough.

If we look around, we formed a global physician network of physicians that understand this disease, that are tracking confirmed unique cases in 35 countries, and you can see we recognize 427 OUS world cases as well as 19 deaths around the world, where we

feel very comfortable that the pathology was known and that these are unique cases. We recognized 5 deaths in the United States as well as 152, giving us approximately 578 cases worldwide that I feel comfortable in.

I believe that the middle column answers, Dr. Li, your question, which is how does the MAUDE database break down by manufacturers? So, we did a collaboration between MD Anderson and Janette Alexander at the FDA in 2017, and we broke down the MAUDE database by manufacturer. You can see Garry Brody's series in the first column, and MD Anderson updated as of this last week, and you can see while all implant manufacturers are represented, Allergan is overrepresented statistically with comparison to the other breast implant manufacturers.

So, if we look at Biocell compared to all other manufacturers combined, it's anywhere from 7.1 to 8.3 times greater than the other manufacturers. And if we look at what's pertinent to the U.S. market, which is Allergan to Mentor, it's anywhere from 9x to 32 times greater than Mentor implants.

The only prospective data that we have to date is Allergan Biocell, 17,656 patients from the CARE trial. And it's important that this is prospective Level II evidence demonstrating, now updated, 8 ALCL cases out of that cohort being 1 in 2200.

It's important to note, out of Memorial Sloan Kettering, Dr. Peter Cordeiro, former chair of the department, as well as Ahmet Dogan, one of the foremost authorities on breast implant ALCL, now reports out of 5,700 cases, which 96% were textured Allergan Biocell, 8 personal cases coming out at 1 in 460. It's important to note that this series is completely reconstructive, and those patients may have more genetic drivers than the general population.

This is all salient information. Note, when you take into account that Biocell has now lost -- did not have renewal of its CE mark, which affects Europe and five other countries

have decided to follow, so that's all of Europe, Israel, Brazil, Russia, Japan, and Australia, being 38 countries to date, Allergan responded saying -- they cited the incomplete routine review and renewal of that file.

If we look at global estimates around the world, I've said just raw numbers, how many were found in each market, Australia and New Zealand has taken the extra step of getting the denominator, sales information, so that when you actually compare, you compare apples to apples. Allergan Biocell coming at 1 in 3,300. Mentor Siltex 1 in 86,000. So, based on manufacturer sales difference, that's a 25.7:1 ratio between Biocell and Siltex.

The Netherlands describes 1 in 69,000 for all implants; however, the Netherlands is approximately a 97% textured implant market, so technically that's textured implant.

The U.S. re-reported in 2017 a rate of 1 in 30,000. I can update that to 1 in 19,000. The U.S. is basically a mixed market of Allergan to Mentor, so a certain proportion of 1 in 30,000 to a certain proportion of 1 in 86,000 adding up to those numbers.

It has risen. A standardized approach to this disease comes from the National Comprehensive Cancer Network guidelines, which now are advocated by both of our major societies, and 2019 guidelines are now updated in the *Aesthetic Surgery Journal* as of this month. I won't go into this in detail, but it now gives a very reliable way to make a diagnosis within these patients, as well as a reliable treatment strategy based on stage of disease. So, pathology diagnosis is made with CD30 immunohistochemistry, as well as anaplastic cells, as well as a single T-cell clone on flow cytometry. All three of those must be present for the diagnosis. By that criteria, that's how we separate a benign seroma, which can be normal, from a patient that has breast implant ALCL, which is abnormal.

If we actually look once we have the diagnosis and we're going to work it up with a PET CT scan, you can see a 16 cm mass growing on the surface of a breast implant in this PET CT scan.

We used to think that breast implant ALCL was two distinct diseases; one was an effusion only, and one was an invasive mass. However, that was in 2016 based on only 19 cases. Today, at MD Anderson, we actually recognize that it's a spectrum of disease going from an effusion infiltrating into a capsule, forming a mass, and then metastasizing to lymph nodes in rare cases for the majority of patients that can be treated with surgery and surgery alone, which is an en-bloc resection of the disease.

And these videos just demonstrate masses growing on the surface of a breast implant, how it looks in pathology. And it's incredibly important to perform the surgery and actually completely remove the disease. There in the bottom you can see that 16 cm mass and the Allergan 410 implant just behind in the picture. These patients were treated with surgery. The top patient did require a new adjuvant-targeted immune therapy.

Complete resection is critical because we do have some cases where partial resection led to retained masses, and in those situations, it does have the propensity for metastasis, as was seen in this patient, that actually metastasized to bone marrow in her body.

What we find is in these advanced cases, there may be histological markers for an aggressive disease. For instance, in that case that I just showed you, it's one of the very few that actually has infiltration of the breast ducts. We've seen this in three patients. One of them got bone marrow metastasis; two have expired. So, this does seem to be an aggressive marker.

When we look at staging of disease, we now see four different countries around the world reporting stage of disease, and what we can see is that the average is that they're all kind of clustering pretty close with the majority of patients being an effusion only and then everybody else somewhere down between. We do feel that surgery and surgery alone can treat approximately 85% of patients, but about 15% will receive -- they'll need adjuvant

treatment, either radiation therapy or targeted immune therapy.

If we look at how patients are treated, we see that 45% get radiation therapy, 60% get chemotherapy, 7% get stem cell transplant, and this speaks to that possibly patients aren't being optimally treated.

I did mention that we have deaths, and we have 19 attributable deaths to date worldwide. We mentioned that on the FDA website it's nine. In that manuscript that we combined with the FDA, we found that approximately 13% of the MAUDE database was for OUS cases, and we think that that's where some of those cases are coming from, 13%. We recognize 5 in the United States and 19. And, statistically, they did have a delay in treatment, and none of them had complete resection of the disease.

We have formed a centralized tissue repository at MD Anderson. It sends over 50 specimens to multiple institutions around the world. I won't go through these in detail, but just to show you some of the research that we've done, this is a collaboration with Boston University where we demonstrated that these patients are not responding to a textured breast implant like the general population. It's marked by IL-13, IgE, and PGD_2. What did I just say? They're having an allergic inflammation to the breast implant, so they're responding in an abnormal way, creating a chronic inflammatory state, on average, 8 to 10 years.

It has been shown that JAK1 and STAT3 driver mutations have been implicated, and in a collaboration that we did with Mayo Clinic, we demonstrated in 36 cases that all of them were negative for DUSP22, TP63, and ALK negative. And all of them demonstrated STAT3.

And so, Dr. Sandler, you asked if there was any markers that we found. So, we have not only CD30 but also interestingly enough CA9, which is only seen in renal cell carcinoma. It does seem to spill into the bloodstream from this disease. Also, 80% will

express PDL1, potentially making the nivolumab a therapeutic target, as yet we have not tried.

It has been suggested a gram-negative biofilm releasing an endotoxin potentially chronically stimulating through a toll receptor may be causing this T-cell lymphoma. I will point out that there is no precedence for an endotoxin leading to a T-cell lymphoma, either in a case report or in a case series, but this is an important theory that's being pursued right now.

We did do a collaboration with Northwestern University where we demonstrated in 822 patients prospectively studied, that they did have a three times higher infection rate with textured implants rather than smooth implants. I'm not sure if that's the chicken or the egg.

We did look in a collaboration with Washington University, do they have different bacteria in ALCL patients, and we found that they did not. They are very similar to the general population, mostly marked by gram-positive *Propionibacterium* and *Staphylococcus*. So, they don't have unique microbiomes.

It's been suggested by some authors that an anti-infective technique would potentially lower the risk, and we were interested in a study which was purported to be by eight plastic surgeons on a 14-year prospective series. However, it was on an anti-infective strategy that was first created in 2013.

Therefore, we looked at the intraoperative techniques of ALCL patients, and we found that if operative technique could affect risk, no strategies have yet been determined to actually lower. And so, patients have received Betadine, have received triple antibiotic, have received 14-point plan, and yet could still develop this disease, which I think is an important factor.

It's also been described it is a macrophage particulate digestion, particulate actually

given off the implant digested by macrophages releasing inflammatory cytokines. This has been purported in orthopedic literature and that those cytokines then stimulate activated B cells and activated Th helper cells. We see that Th helper cells are the precursor cell for this, which is Th1, 2, and 17. And what we haven't talked about today is that there is, to date, nine B-cell lymphomas arising around breast implants, so also possibly through this same mechanism, though I'll be quick to point out all of those were EBV positive.

Is type of texturing predictive for breast implant ALCL? Well, a number of different semantics have been used to describe different types of implants, and we've seen over the past year biocompatibility studies are coming out saying how does roughness and implant characteristics affect hydrophobicity, macrophage polarization, ability for bacterial adherence?

And what we've seen is a number of different classifications come out. These are five different classifications coming out just in the last 8 months, all about breast implants. ISO classification is probably the one most used by regulators, most recently updated in June of 2018. And ANSM built very closely on ISO except for from the 2007 version. And then we can see several peer-reviewed scientific publications on the same subject. None of these have been validated for ALCL occurrence, but what I can tell you is that there's no ALCL cases in the top row. There is more ALCL cases in the bottom row, and then the middle row statistically has less than the bottom row. However, I can't tell you which one best predicts for ALCL.

So, in general, we try our best not to frighten patients but to inform them. It's important to realize that this is uncommon and that it does have a very good prognosis when caught early. I would say that as part of surgery consent, it is important to give them the package insert. A checklist would help. ANSM did recommend black-boxing as part of their recommendations. And you may want to include the CE mark withdrawal now affects

Biocell sales in 38 other countries, save only for the United States and Canada.

Retroactive notification of patients has been suggested. For many institutions, it is incredibly onerous and not possible. Memorial Sloan Kettering has done it, as you can see in the document on the bottom. Penn State has done it as well. And for the most part, patients did not freak out; they were able to take this information and digest it in an appropriate manner.

And I will point out that plastic surgery is really coming together, and I'm optimistic about our grasp of ALCL. Fifty-five authors this month published 16 peer-reviewed articles in our two major journals, and you can see that all of them talk about the major pathogenesis of this disease risk, everything that we know on this disease right now. We're trying our best to stay ahead of this for the sake of our patients.

So, in conclusion, breast implant ALCL is a lymphoma based on pathology and clinical course.

NCCN guidelines have risen as the standard of care for the diagnosis and treatment in an evidence-based approach.

Current research focuses on determining genetically at-risk populations and stratifying inflammatory reactions to different types of texturing.

I've shown you a tremendous amount of data. Data is neither good nor bad. Data cannot fail us. The only way that it fails is if we fail to learn from it.

Thank you.

(Applause.)

DR. LEWIS: Thank you, Dr. Clemens.

We'll now proceed to a discussion of autoimmune syndrome induced by adjuvants, titled ASIA and Breast Implant Illness, to be presented by Dr. Jan Tervaert.

DR. TERVAERT: Thank you. Good afternoon. I would like to thank Dr. Ashar and the

Panel to have me invited here. I'm very excited about it. Although it took a long trip before I came here because it took me 2 days to come from Edmonton to here because of planes that have problems. So today I will talk about ASIA and breast implant illness. I have nothing to disclose. I am not supported by the industry, I'm not supported by the FDA, I'm not supported by Health Canada, so I'm totally free of speech, so to say.

I speak in front of surgeons, and I am a Professor of Medicine and Immunology, I'm a Professor of Rheumatology in Canada, and Division Director in Edmonton, but I'm more a doctor, a doctor for patients with rare autoimmune disease that are not immediately diagnosed. And that's a practice that I have performed more than 30 years now.

But speaking in front of surgeons, I have to express some love with the surgery. I'm trained as a nephrologist, so there we had great success with kidney transplantation. Dr. Murray got the Nobel Prize for it, but he realized already that you had to be careful with the immune system, so he did a transplantation in an identical twin. Only in '61 when azathioprine was used and later on ciclosporin, it appeared also possible to transplant from one patient to another. And now we have the great success of all those transplants.

About in the same time, Dr. Cronin and Gerow performed silicone breast implants, and they thought okay, this is inert, so we don't have to fool the immune system. The immune system doesn't react at all. They did not get the Nobel Prize because already a few years later it became clear that implants are not inert. They react with the immune system. And later on, autoimmune diseases were reported in these patients.

So, the history of silicone breast implants is connected with many different affairs, like the PIP affair in Europe, Silimed affair in Holland where they detected D5 and fibers in the implants, and more recently, the ban on the textured Allergan implants.

So, what about the frequency? There is not a lot of good data, but we know in the Netherlands and in the United States about 4% of the women do have breast implants, and

worldwide, at least 10 million breast implants are being placed.

And Wikipedia still says these silicones, they are optically clear and, in general, inert and nontoxic. So, my goal of my talk is now is that true?

Well, we know already for a long time that these breast implants cause immune activation. In a recent article, Caldiero, it was stated that more than 50% of the women finally get some capsular formation, and this capsular formation more often occurs in smooth implants and less often after implantation of textured implants, and that's why, in the Netherlands, as you can see on the slide, there's nearly only textured implants being used.

So how does that look? What is that capsular formation, actually? Well, in vitro, silicones do not activate T-cells. But in these patients, if you go into the capsule you see many activated T-cells, and by a FACS analysis of the group of Innsbruck, they showed that these T-cells are mainly the Th1 and the Th17 cells and that the regulatory T-cells there fail to produce regulation. So, this is the perfect circumstance to develop an autoimmune disease.

How does that work? Well, we know that if we implant a biomaterial in a body, that immediately there's proteins attached to the implant and mast cells are being activated so that inflammatory cells are recruited, like neutrophils and macrophages, and that inflammatory products now are being released and that cell death occurs, and cell death is the primary driver of an autoimmune disease.

Here you see it in a different way, the studies by Tang, who really showed that histamine is one of the first phenomenon that you can see in the activation of the phagocytes. So, if you block histamine in animal models, you can have less recruitment of those phagocytes.

So, there is clearly activation of the immune system. There's capsule formation.

There's ASIA or breast implant disease. There's the immune system that cannot cope with all the activation, so that we see immunodeficiencies and immune systems make mistakes if they're constantly activated. One of the mistakes is an autoimmune disease, but another is that you have exaggerated allergies and sometimes you get monoclonal proliferation such as an ALCL.

So how does this occur? Well, we know that if the implants rupture, that's a major cause of silicone coming free into the body. But we also know that silicone breast implants may bleed, so that if there's no rupture at all needed to have silicones migrating to your body, as you can see, for instance, on the slide, then you have these axillary lymph nodes where silicones are clearly present without any rupture of the breast implant.

So, we know most of the implants will finally rupture, although for the newer ones, we don't have good data yet. But, in addition, the gel bleeds and there we have no figures at all.

So, what is ASIA? What is breast implant disease? We defined this as your exposure to the breast implant in combination with clinical findings and then removal of the agent induces improvement. If you do biopsy, you see granulomatous inflammation.

In addition, we have some minor criteria with the development of other antibodies and other clinical manifestations, so irritable bowel syndrome. We have specific HLA associations, and we have the evolvement of real autoimmune diseases.

So, what are the ASIA symptoms? Patients generally are always tired, and they're already tired when they wake up, and they have clear post-exertional malaise, meaning that if you do a day very much, the next day you lay the whole day in your bed. There's widespread pain, there's myalgias and arthralgias, there's cognitive impairment, there's feverish feelings and sometimes real high fever, and there is very prominent sicca symptoms. So most of these patients do have severe dry eyes and dry mouth.

And, curiously, there's very strange neurological symptoms. Some patients have classic stroke at a very young age without the risk factors for a stroke, or they have multiple sclerosis-like symptoms. Physical examination reveals generally Livedo reticularis, patients have Raynaud's phenomenon, and there's nearly always lymphadenopathy, axillary lymphadenopathy, but also cervical and inguinal.

So, it takes some time to take all the complaints that these patients have. That's why I think it's better for a rheumatologist than for a surgeon.

So, we compared the symptoms of these patients in a current series and a post here from Houston in 1994, and what we found is that the findings are actually very comparable. So, despite all these new developments by the industry, we see the same symptoms in our patients.

Importantly, if we look at what kind of patients do develop ASIA, we found that 75% of the patients do have preexistent allergies and some of these patients did have preexistent autoimmune diseases. So that's the warning that's in Holland and nowadays is done to the plastic surgeons, don't -- be very careful to implant a patient with silicone breasts if they have preexistent allergies.

So how often does ASIA now occur? There's no good studies. I'm sorry. We tried a little to answer this question. So, what we did is we looked at the patients that have been operated in the south, southern part of the Netherlands, and we compared them with France, to healthy controls of these patients, and we compared it with patients that are registered as breast implant patients in the Netherlands. Totally, we invited 231 females. Of the 231 females, 221 responded.

And what we found is that if you compare the healthy controls with the patients that do not have complaints registered at any registry at all in the Netherlands, that we see a four times more increase in ASIA. And the patients that think they have breast implant

disease, about half of them clearly had the criteria for ASIA.

So is this mass somatization, which is published, and any plastic surgeons actually point to Reid et al. This is just the ladies think of it by themselves. Well, a proof that it's not the case is, for instance, this patient that died and said I give my body for the scientific purpose, and we did a long-time discussion of how to detect silicone. It's very difficult in a human body -- made it with three phase techniques clear that there is a lot of silicones in this lady. Not only in the lymph nodes with granulomatous inflammation around it, but more seriously also in the brain and the nerves; everywhere in her body there was clear presence of silicones. But this is only one patient.

And now we have the second patient. So, she's still alive. That's a patient that I saw with ASIA and that had breast implants that also quite soon after her first breast implant she developed capsular formation. She had very widespread pain and could not speak well in periods and had paresis of the left leg with many pains. Nobody knew actually exactly what kind of diagnosis to put on. So, she was at the experts in Leiden who said, okay, this is CRPS with acute dystonia, and she got a ketamine infusion with some success, but finally the pain was unbearable, and the doctor said, okay, let's do a left leg amputation. And the breast implant was also explanted.

And so, recently, Henry Dijkman, who is the developer of this silicone-based research, could detect in that leg a lot of silicones surrounded by granulomatous inflammation exactly at the place where the muscle was necrotic. So, this is the second case that really demonstrates that there is migration of silicone throughout a body and the nerves, vessels, and brains.

Another factor that's important for the ASIA syndrome is it's associated with autoimmune diseases, but that's a long discussion, but we think the following is true. So generally, autoimmunity, you only get it when there's many different environmental factors

and genetic factors present, and silicone breast implants could be only one of these factors.

So, I would like to present one case, a 39-year-old lady who had breast implants in 2006 and new implants in 2010. She had 5 years of intermittent fever and fatigue, joint pains, myalgias, sicca complaints, concentration problems, cognitive impairment, and recent onset Raynaud's.

So, the question is now is there an increase of autoimmune diseases in these patients? First of all, is there animal data? There is. So, you can put a breast implant in mice and then look whether there is more autoimmune diseases. And, typically, if you do this in mice with no genetic predisposition to develop an autoimmune disease, nothing happens. But if you put it in mice that are well known to develop autoimmune diseases, then the autoimmune diseases come earlier and are more severe, and that's why we think it's an adjuvant effect. This is also true for the collagen-induced arthritis.

So, this is how it works. It's the dendritic cells who are driven then to become major dendritic cells, and then they're allowed to stimulate immune systems so that the autoimmunity can occur.

So, in my population, when I first saw the ASIA in our patient population, we saw a lot of problems. So out of the 32 patients, half of them had developed an immune deficiency, which is a very rare disease generally, but here 50% of my patients did have it and about 50% of the patients did have systemic autoimmune diseases. So, this can be very different autoimmune diseases. I'm a specialist in vasculitis, so therefore, some of them had vasculitis, but also connective tissue diseases, other autoimmune diseases like Crohn's disease and sarcoidosis, multiple sclerosis and more organ-specific autoimmune diseases. In my later studies, I've see now some 500 patients; this is still true that there is many autoimmune diseases, different autoimmune diseases occurring in these patients.

So why does the literature say there's not an increase? Well, we have to go back to

the meta-analysis by Balk, where he said, okay, there's nearly -- all previous studies are not adequately adjusted or not adjusted at all for potential confounders. There is an increased risk, actually, from all these previous data for rheumatoid arthritis and for Sjögren's disease. And associations may be driven by self-reported disease, so not always the doctors have confirmed the diagnosis.

In all cases, epidemiological studies until 2016 were inconclusive. We can't say they're safe; we can't say there's an increase of autoimmune diseases based on these studies. So here you see, for instance, from Balk's review, an increased risk for Sjögren's disease nearly three times higher.

So, more recently, Dr. Clemens reported also the increased occurrence of Sjögren's, and then he had an odds ratio of nearly 8. However, all these studies were basically patient-mentioned diseases.

So, therefore, we went to Israel where they have an excellent registration, especially for autoimmune diseases, and we looked at 25,000 patients with breast implants and compared it with 100,000 ladies who did not have breast implants, and we clearly show an increased risk of autoimmune diseases, as you can see, and also for Sjögren's disease. Sarcoidosis or systemic sclerosis were the main factors.

And here you can see how it works. So, if we compare them, we see that it's during late development of autoimmune diseases. Generally, after 10 years you see the increase more drastically occurring, compatible with the fact that then they are bleeding, the breast implants, and finally rupturing. And we calculated the risk to be 45% higher in patients with breast implants compared to the general population.

So, this is how we think it works. There's many factors before you get an autoimmune disease. The breast implants are one of them, but there may be other factors playing a role as well, just as vitamin D and smoking, etc.

So, let's go back to our patient. Our patient did have positive antibodies to nuclear antigens. They have Sjögren's syndrome antibody A positive and, well, we didn't make a definite diagnosis of Sjögren because then you do a lip biopsy and we didn't do that. We said, okay, you have to go for therapy, you have to remove your breast implants, you have that ongoing fever all the time, she was hospitalized five times in an academic hospital without a diagnosis, and so you go for the explantation. We know that explantations actually are effective in about 50 to 75%. In a review that we did, we had positive 75%. It's effective as long as tolerance is not broken. If you have already an autoimmune disease where tolerance is broken, then you also have to treat the autoimmune disease, but generally then the treatment is more easy than when you leave these breast implants in the female.

So, this is my experience of the first 85 patients with explantation. You see also a success rate of about 60% in the patients without a definite autoimmune disease.

So, what did we do with the patient? We removed the breast implant, and we did total capsulectomy. As you can see on this slide, if you do partial capsulectomy, patients have more symptoms persistent than when it's possible to remove everything.

So, she deteriorated after surgery temporarily, wherefore she was given some steroids, and then we started maintenance therapy with doxycycline, and after that, she didn't have any fever periods anymore with a follow-up of 24 months.

So, in conclusion, I think that I hope to convince you that biomaterial implantation can result in systemic symptoms with signs of immune activation and/or recurrent infections as a result of immune deficiency because the implant is never inert. It is recognized by the immune system.

And patients with systemic symptoms often have preexistent allergies, preexistent fibro and/or preexistent autoimmune diseases, and therefore, we should warn these ladies

very well that they must be very well convinced that they need the breast implant and that we doctors actually say don't do it.

So, silicone breast implants, mesh and mineral oil fillers can all cause ASIA, and in these patients, more often autoimmune diseases occur, but also immunodeficiencies and severe allergies and possibly -- well, in the meeting, yes, convincingly, also lymphomas and explantation of the breast implant results in 75% of cases in decrease of symptoms.

So, what does it mean? We need to educate our patients, but also there is now in the Netherlands a meeting last week with the House of Representatives where many representatives actually asked the Minister of Health to ban the silicone breast implants from the market. Why? Because there is the principle of precautionary, and precautionary principles have left the scientists to remove genetic manipulation of humans after the Chinese doctor manipulated the genes.

After two airplanes, it was decided that the airplanes should be banned for a while until it's proven that it's safe. How many patients do we have to prove that there's migration of silicone through the body before we can say --

(Applause.)

DR. TERVAERT: Before we can say that it's -- that we need more studies to prove safety of these breast implants.

So, these are the people that helped me very much. So most of them are plastic surgeons. Professor Rene van der Hulst from Maastricht. Rita Kappel is a plastic surgeon in the Netherlands. Maartje Colaris and Mintsje de Boer are both residents now in plastic surgery. And Yehuda Shoenfeld and Abdulla Watad are both immunologists from Israel.

These are the articles that you can read if you want to learn more about this issue.

I came here and I said we did some 2 years -- 2 days to be here. I came with my son of 13, and he's very good in computer science, so he makes this for us.

(Laughter.)

DR. TERVAERT: Thank you very much.

(Applause.)

DR. LEWIS: Thank you, Dr. Tervaert.

Our last presentation of this session will be by Dr. Diana Zuckerman from the National Center for Health Research, who will speak about analysis of symptoms and diagnoses of 400 women before and after having breast implants removed.

DR. ZUCKERMAN: Thank you very much for inviting me to speak today. I want to start with a disclosure. The National Center for Health Research does not accept funding from medical device or pharmaceutical companies, so the center has no conflicts of interest. My father worked for Johnson & Johnson most of his career, and I inherited stock in J&J when my parents passed away, and so to make up for that bias, I do want to mention that Mentor lost track of 85% of their patients in their postmarket studies, and that is the worst track record of any of the manufacturers.

So, my perspective is as a person trained in epidemiology from Yale Medical School. I was on the faculty at Vassar and Yale, was a research director at Harvard before coming to Washington, and I'm a peer reviewer for multiple major medical journals. So, I take research very seriously, and I am going to talk about the research that we've recently completed.

I want to start out by saying that implant manufacturers, when they submitted their studies to the FDA, they intentionally excluded women with a history of autoimmune disease from those studies, and we know that because they admitted it and because -- and as a result, the manufacturers' breast implant booklets, which are required by the FDA, currently say some variation of this: "Caution: Notify your doctor if you have any of the following conditions as the risks of breast implant surgery may be higher." And then the

first thing they list is "Autoimmune disease (for example, lupus and scleroderma)." Unfortunately, the FDA website does not include that warning, and women tell us they haven't heard it.

In 2005 when FDA looked at studies submitted to them by the manufacturers, the Allergan data from 2 years found an increase in the following connective tissue disease categories: general issues, muscle weakness, joint pain, and skin symptoms, meaning things like rashes.

Similarly, for Mentor, there were significant increases in fatigue, exhaustion, joint swelling, frequent muscle cramps, joint pain, and fibromyalgia among augmentation patients, and in both cases the statistician made it clear this was not due to age. So, they compared women just before getting breast implants, those same women 2 years later, controlling for age.

And yet, as you know, the FDA, the manufacturers, and the plastic surgeons have continued to state there's no definitive evidence of systemic health issues from implants despite those significant increases in symptoms that were submitted to the FDA more than a dozen years ago.

There have been other studies of systemic illness, and you've heard about quite of few of them. I want to specifically mention the Tufts report, which was quoted a few times, because the Tufts report is based on a summary of other studies, and those other studies have some major flaws. Many of the studies included women who had implants for less than a year or less than 2 years or less than 3 years, and as you've heard, these symptoms develop later. Many of the studies had small numbers of women. Most of the studies were looking at rare diseases but not studying symptoms. And some of the studies even focused on hospitalization records, and women with joint pain and mental confusion aren't going to be hospitalized, so hospital records are not a good way to measure them. And the other

ones mostly looked at medical records which did not necessarily include the symptoms that the women were reporting. You've just heard about the Israeli study that was published last year which did find a significant increase in Sjögren's syndrome, multiple sclerosis, and other disorders.

The National Center for Health Research conducted our own study. We have already been helping over 6,000 women who had reached out to us asking for help getting insurance coverage for medically necessary explant surgery. These were women who wanted to have their implants removed and not replaced.

So, we contacted the 792 of those women who we knew had removed their implants in 2016, 2017, or 2018. Keep in mind, we were already familiar with their medical problems, we had seen their medical records and/or their letters of medical necessity to their insurance companies, so we knew that these women were very sick, and they were desperate for help because they couldn't afford to get their implants taken out; they didn't have the money to do that.

We emailed them with a link to an online survey starting this past November and ending in January, and 57% of those women, 449, filled out the questionnaire.

We asked the women why they wanted their implants removed, and 54% said because of breast pain, 34% said because of breast hardness, 27% said because of rupture, and 85% said because of other health issues. I'll talk about that in a minute.

Here's our Table 1. It just gives the usual typical information about demographics and some information about their implants. I will go over the highlights.

The women ranged in age between 24 and 82 years old with a mean of 49; 93% were white. Three out of four had implants for at least 10 years, and only 21% had more than two breast implants; in other words, they had gotten implants, and they had been replaced. Forty-eight percent had saline implants only, 39% had silicone gel implants only, and 12%

had had both. Again, those are women who had more than one set of implants. And these were all augmentation patients.

Then we asked how long they had had these health symptoms before they had gotten their implants removed, and you've heard a little bit about this today, that a lot of times these women have symptoms and problems for years before they get their implants out for a variety of reasons. For the women in our study, 59% reported that their symptoms lasted at least 5 years, so that's the red and the blue in that pie chart.

Twenty-eight percent reported that their doctor told them after their implants had been removed that their implants were ruptured, so that's a definitive diagnosis. Fifty-six percent reported that they had had either an en-bloc surgery to remove -- had to have an en-bloc surgery to remove their breast implants and an additional 26% reported having a total capsulectomy. For those of you who don't know, these are the ways of getting the maximum amount of the scar tissue removed. And since the silicone and other chemicals can get into that scar tissue, many of us believe that that's very important to get as much of the scar tissue out as possible.

We also asked about family history. Sixty-nine percent, which seems like a lot, reported some kind of family history of autoimmune disease. You know, there's some confusion about what are autoimmune diseases. We gave some examples, but you know, we can't say for sure that that's exactly right, but it gives you some sense of what's going on. Only 3% of the women reported a personal history of autoimmune disease, but 12% had said they had some possible symptoms before they got their breast implants. And then just over half, 51%, reported that they were diagnosed with an autoimmune disease after getting their breast implants.

We asked them exactly what symptoms they had had, and this was an open-ended question, we didn't want to influence it in any way, so it was open-ended, and then we

categorized them as best we could. The most common symptom was joint and muscle pain or weakness. Number 2 was fatigue. Number 3 was what the women call silicone brain fog, which is memory and concentration issues; you've heard about that as well. Number 4 was anxiety and depression. You know, I have to say, you never know, is that an autoimmune type of response, or is that a response to all the other health problems that they're having? Number 5 was hair loss. Number 6 was breast pain. Number 7 was rashes and other kinds of skin irritation and skin problems. Number 9 [sic] was general body pain, overall body pain, fibromyalgia type of problems. And Number 9 was gastrointestinal problems. And those are really the most common. There certainly were others, dry eye, allergies, and other symptoms.

We then asked them, you've now told us what your symptoms were, did they get better, worse, or about the same since having your implants removed? And you can see that almost 61% reported that they got much better, 29% that they got somewhat better, 8% said they stayed about the same, and just under 2% said they either got worse or much worse.

And then we tried to figure out could we predict who was going to recover more. So, we looked at all the variables we had and independently looking at each one, we found all of these were statistically significant predictors. And so, for example, having implants for more than 10 years, those women were less likely to fully recover. Having had autoimmune symptoms before they got their implants also reduced the chances of the women recovering. Having a rupture or a leakage as the reason for having their implants removed also predicted a less good outcome. And some of the other things are a little bit confounding, so I won't go into that, but the last one, en-bloc or total capsulectomy for removal predicted a better outcome and you can see highly significant.

But as many of you know, if you look at enough variables, something's going to come

out significant. So, we threw them all together into a logistic regression so that we could control for that confounding, and what we ended up with was two variables that still predicted when everything else was controlled, and one was a family history of autoimmune disease, which predicted a less good outcome, and then en-bloc or total capsulectomy removal, which predicted a better outcome after removal.

So, in conclusion, we've talked to and helped more than 6,000 women who wanted to get their implants removed but were having a hard time because they couldn't afford it. And many of those women had problems for many years before they finally got their implants removed.

The symptoms and the diseases that the women are reporting fit in very well with what's called breast implant illness, and they're very similar to the same kinds of symptoms that have been reported in studies submitted to the FDA in 2005 as well as reported by more than 70,000 women on Facebook.

A family history of autoimmune disease and the number of years with implants significantly predict a poorer recovery after explant.

And how implants are explanted, how much scar tissue is removed, and how carefully seems to have a significant impact in improving the likelihood that women will have a good recovery.

So, this has clear implications for some of the issues you'll be talking about and we have been talking about, and informed consent is a big one.

So, we conclude that women need to be warned about the possible role of family history and personal medical history. Obviously, our sample is not a random sample of women; it's a sample of women who wanted to get their implants out and were able to get them out. But for those women, and there's thousands of them, there seems to be a relationship with these, family history and personal medical history.

We believe that women need to be informed that systemic symptoms may be caused by implants. Again, this is not a random sample of patients, but there are thousands of patients who have contacted us with those problems as well as the 70,000 women on Facebook and other social media and the women that you've heard from today.

We think that women need to be informed that an appropriate explant surgery can significantly improve their health because we hear from the women that they're told by their doctors it has nothing to do with your breast implants and taking your breast implants out won't make a difference. What we always tell women when we talk to them is there's no guarantee that taking implants out will improve your health but that for a lot of women, it does.

And then, finally, we're very concerned about what information is going to be in the registries. Registries could be a very good source of data, but only if they include some of the things that are not yet in there. One of them is women's self-report of systemic illness or any other kind of medical reports of systemic illnesses. But also, currently, the registry is focused on operations and reoperations and explant operations, and what we're finding is that many women just can't afford it. So, if our registries only look at the women who have had those operations and thousands of women aren't getting them, it can't really provide the information that we need to make progress in figuring out how many women are getting ill and what's happening to them.

And that's all, and of course, I'm happy to answer any questions as I'm sure the other panel members. Thank you.

DR. LEWIS: Thank you, Dr. Zuckerman.

I'd like to ask now Dr. --

(Applause.)

DR. LEWIS: I'd like to ask Drs. Pusic, Clemens, Tervaert, and Zuckerman to please

come to the podium so that they can respond to questions from the panelists, and I'd like to ask the panelists to ask any clarifying questions they need to. We're running a little behind schedule, but we will basically move the schedule backward 15 minutes, and then we will not have clarifying questions following the public comments. We will have the full hour for public comments, but we will not have the clarifying questions after that. We will have the clarifying questions presently for these four presentations. So, let's begin over here.

DR. LIPPMAN: Thank you.

First of all, I think all four of the presentations were excellent; thank you so much for them. Dr. Clemens, you spoke a little quickly for me. In your recommendation you didn't seem to make a point that seemed to be in your data about differences in risk for ALCL with different implants. I believe you said 1 out of 3,345 for the Allergan one in the Australian study, and for the Mentor, it was 1 in 86,000. Do you stand by those data, and if so, why wasn't that part of your recommendation?

DR. CLEMENS: Yes, I stand behind that data, and that was produced by Anand Deva, and he found that 26:1 ratio between Allergan versus Mentor. When we had sales information for the United States, we found a 9:1 ratio. So, for every 10 cases, 9 being Allergan Biocell.

DR. LIPPMAN: And do you have a conclusion?

DR. CLEMENS: That it is not just texturing versus not texturing. It does seem to be manufacturer specific. So, when we talk about risk, we really should be talking about risk per manufacturer.

DR. LIPPMAN: Thank you.

(Applause.)

DR. LEWIS: Dr. McGrath.

DR. McGRATH: Yeah, I would just say that it's probably the total surface area that's

more relevant than to question the manufacturer. Just to clarify that, it's the amount of texturing.

DR. CLEMENS: That's one that's been theorized by Anand Deva, is that it's surface area.

DR. McGRATH: Yes.

DR. CLEMENS: We've seen five different classification systems come out just in the last 8 months. Some have classified it by bacterial adherence to the surface and some have classified it by surface area. Some have further classified it by how do you determine surface area, whether it's spectral CT, whether it's by SEM, whether it's by -- so there's a number of different ways to actually get at surface area, none of which have been validated in a prospective series saying, you know, this actually predicts for the rate of ALCL, but we are seeing more and more research looking into trying to delineate different types of texturing and what might be different between them.

DR. McGRATH: My question to you, you talked about genetic or immunologic susceptibility and very early research and some early data, particularly, you know, about -- oh, perhaps you mentioned some germline mutations and so forth. Are we at a stage where anything is yet cost effective enough and presumably going to be predictive enough to start talking about actually doing this testing outside of a research situation or a clinical trial?

DR. CLEMENS: No, not yet. Not today. That would be our goal within a couple of years. We've recognized, through a collaboration with Mayo Clinic, that they do have higher rates of JAK1 and STAT3 mutations and some of those were determined to be germline mutations, so effectively being born with a genetic predisposition. But we also published in February a study on HLA predisposition, that it could actually predict when compared to the general population, so while some of these are interesting, maybe

potential targets in the future to identify susceptible populations. We're not at the point where there is a lab test that we can perform today and say this patient has X percentage of developing this disease.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: Dr. Pusic, just a quick question. Could you clarify for me what the relationship is between the NBIR and PROFILE?

DR. PUSIC: They're both registries run by the Plastic Surgery Foundation. PROFILE is a rare disease -- is a registry of simply cases of BIA-ALCL, whereas the National Breast Implant Registry is a registry open to all patients, all women having breast implants placed in the United States.

DR. BALLMAN: So why isn't that a sub-study of the NBIR? As you mentioned, there's going to be some focus sort of, you know, of studies planned in the future.

DR. PUSIC: Good question. It's really historic in the sense that we started working together with the FDA around PROFILE and then recognized the need for a national surveillance system.

DR. LEWIS: Dr. Sandler.

DR. SANDLER: Dr. Pusic, a great presentation. And these registries are big, and it's very noble work, but I'm going back to something Dr. Lippman mentioned earlier. What's going to be your appropriate control population when you're looking at things that you identify in the NBIR, and how will you know whether it's different than what you would expect in women who never had a breast implant?

DR. PUSIC: Um-hum. Yeah, I think there's different ways that we're going to try and delay on this, I think it depends. And we also can lean on thinking about the experience of other registries in completely other experiences. In looking at, say -- and I'll speak first about sort of a device that's a problem. We know that if we're following say, PROs, we may

see a change in symptoms relative to benchmarking of one device relative to another. The example might be the Australian experience when they -- in orthopedics, in hips, where they saw a rise in pain before they started to see a rise in reoperation around metal-on-metal hips. So, I think part of it is benchmarking and watching for safety signals. But you're absolutely right in terms of the consideration of what's our control population. To some extent, I could envision us doing sub-studies where we used patients as their own control, so if we're looking in the context of symptoms, a sub-study where we are evaluating baseline symptoms prior to breast augmentation and then following those patients forward. I think ideally, yes, we would also do a sub-study where we find just the right patient population that matches our patient population, and I think that there is the potential, as was done in Israel, I think that maybe the opportunity to look at different insurance databases and different systems.

So I think there is -- it's not the -- it's not an easy patient population to find and that's why we haven't found it yet, but I would say that it's also trying -- and also the international experience of multiple registries that are all looking at this issue and recognizing now that we're all using the same data definitions, which is also helpful.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: Dr. Pusic, you were commenting that the registry could read the barcode of the implants and so that would be a way to get all the implants entered. So, are the patient-reported outcomes linked to the barcode of the implant they got?

DR. PUSIC: Correct. So, where we will -- we are just starting our PRO work in the National Breast Implant Registry, but yes, that unique device identification data so we will know that that patient, that as she is ultimately reporting on her symptoms over time, we will have accurate information about what device she has.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: In 1992 the FDA banned the use of silicone gel-filled breast implants for general use. In the years following, there were many studies, and subsequently, the Institute of Medicine, as Dr. Zuckerman mentioned, came out with a statement saying that silicone gel does not cause systemic disease in humans. And that was, in part, the basis for the re-approval of silicone implants in 2006, and you are suggesting or asserting that silicone gel-filled breast implants do cause systemic disease in people. It sounds to me like we're going back to the early '90s. Can you tell me why were we wrong before? Was the data inadequate? Was the science not mature enough? Why is it different again now?

DR. ZUCKERMAN: Yeah. No, thanks for asking that question. The Institute of Medicine report actually only had 17 studies pertaining to anything related to autoimmune or connective tissue diseases, and they did not conclude that breast implants didn't cause these illnesses. What they concluded was we don't know. There's not enough evidence to draw conclusions; we need larger studies. If you look at their report, which I've read and scrutinized rather extensively, the studies really did include things like 250 women who had implants for a year or two. I mean, the studies at that time were not very good, and a lot of them could not -- did not have the power, the statistical power to determine rare diseases, which is mostly what they were looking at. And those are some of the same studies that were included in the Tufts report as well.

So if you look carefully at the studies yourself, I think you'll be surprised to see how small some of them were and the fact that -- I mean, there was one study, for example, that had women who had had breast implants for at least a month, and obviously, that's just not a long enough time to see, you know, what kinds of symptoms were developing.

(Applause.)

DR. LEWIS: Dr. Rogers.

(Off microphone comment.)

DR. LEWIS: I'm sorry. Excuse me, yes.

DR. TERVAERT: The short answer, there is four factors that prove causality. One is the animal studies. Second, which is new, is the explantation data that are not -- were not present in 1992. The third one is that the proof of silicones elsewhere in the body could be demonstrated now. And the fourth, of course, there are a lot of epidemiological studies that appear now recently with a good amount of patients. In the past, they were just too small, and if you have a rare autoimmune disease, you can't detect anything if you just study 1,000 or 2,000 patients. You need those 25,000 patients as we calculated in our Israeli study.

(Applause.)

DR. LEWIS: Dr. Rogers.

DR. ROGERS: This question is for Dr. Pusic. My question has to do with the utilization of the registry and it's -- first, is it a voluntary participation?

DR. PUSIC: It is voluntary participation.

DR. ROGERS: And what do you estimate is the percentage participation if you were to give a percentage of the implants that were placed?

DR. PUSIC: Right now, low, because we are just -- we started the registry in October, so we --

DR. ROGERS: What does low mean?

DR. PUSIC: We have 200 surgeons participating since October.

DR. ROGERS: And that would represent what percentage of implants?

DR. PUSIC: So, we are a society of 8,000 surgeons, not all of whom do breast surgery. We are in that -- in the Australian example that I showed you, we're in that phase here right now where we're still just getting going in terms of ramping up. I think right now we are probably -- if I had to guess in terms of the absolute numbers, we would be in, you

know, the single percentages of implants being placed in our first -- less than 6 months of being operational. The goal though, and this is with my -- my plea to this Panel is, is that we do things that set the bar. The participation in a national breast implant registry is the standard of care, and with that, as we've seen in Australia, as we've seen in the Netherlands and other countries, then we can really bring all of the community of surgeons together to participate in a registry. And it's also our hope with device tracking -- and right now device tracking, which is federally mandated, it will not be necessary to -- necessarily go to the National Breast Implant Registry to fulfill device tracking requirements. But, ultimately, the hope would be that this would be the mechanism and that that, again, would allow us to potentially capture 90 to 95% of all the surgeons that are putting in implants in the United States.

DR. ROGERS: So, your wish list would be that this would be required at the time of implantation for the implants to be registered?

DR. PUSIC: It would.

DR. LEWIS: Dr. Pusic, I'd like to just continue along the same line of questioning. You may have stated this and I missed it, but are you projecting that you will take patients from the time of implantation, not reoperation, and record the data beginning with the implant?

DR. PUSIC: Absolutely. From the time that a patient -- so the first implant procedure and then also subsequently any reoperations.

DR. LEWIS: Correct. And since there are about 400,000 implants per year, what fraction of that would you anticipate you'll be able to get data on?

DR. PUSIC: I hope that we would get 90, 95% of that data, and I think that's what we've seen from these international experiences, that that is possible.

DR. LEWIS: And will the registry potentially have funding to support that, because

you're talking about -- I mean, that's 1,700 a day, basically, that are coming in. That's a massive data collection effort.

DR. PUSIC: Correct. I think it's a massive data collection effort, I think it's a necessary data collection effort, and I think -- and we have used a stakeholder model of funding, and that model will continue.

DR. LEWIS: Thank you.

Yes, Dr. Jaffe.

DR. JAFFE: I have a question for Dr. Clemens. You mentioned some of the mutations in breast implant-associated ALCL and involving the JAK/STAT pathway. Those are similar to what's seen in a large subset of systemic ALCL, both primary cutaneous and systemic. So, it suggests that perhaps the diseases are related, but it may be that the clinical behavior of the breast implant patient is influenced by the microenvironment or -- and the site of disease. But you also mentioned that you -- that there was some evidence that there were germline mutations in some of those patients, and I'm not aware of that published data. Do you have that citation?

DR. CLEMENS: Yeah. So, Piers Blombery found a germline mutation, and then Andrew Feldman at the Mayo Clinic, he's demonstrated some. I'm talking just a couple of cases, though, at this point. So JAK1/STAT3 mutations have been determined. Most of them appear to be spontaneous mutations, and there's been almost -- very few studies where they actually collected blood specimens and tumor specimens to even determine if it was a germline or not. But the Piers Blombery manuscript, which was by Miles Prince, does report a germline mutation.

DR. JAFFE: Okay, but is that in the Feldman paper from *Blood*?

DR. CLEMENS: That's correct.

DR. JAFFE: It's not in that paper?

DR. CLEMENS: No, that one just looked at STAT3 expression and in 29 patients.

DR. JAFFE: No, it also looked -- it also looked at the mutational profile.

DR. CLEMENS: Okay. You'll have to excuse a plastic surgeon talking to a hematopathologist expert on the subject. But, yes, I usually defer to Dr. Feldman in my collaborations with him.

DR. JAFFE: Okay, thank you.

DR. LEWIS: Dr. Anderson.

DR. ANDERSON: Also, a question for Dr. Clemens. In the NCCN guideline that you wrote for the workup of breast implant-associated ALCL, it calls for patients with physical signs, effusion, and then an ultrasound. Any effusion gets an FNA, and I'm reading this and I'm wondering if we're doing more screening and more testing, if I had someone who was asymptomatic but on an ultrasound a little bit of seroma fluid could be seen, I would imagine that's kind of common. But is that the patient that would end up getting -- that would be a lot of FNAs, or what are your thoughts on that?

DR. CLEMENS: Yeah. So that's a critical point that we need to clarify. Every single patient has 10, 15 cc of fluid around a breast implant. That's asymptomatic. That is not a symptom in and of itself. Those patients are not screened or not tested. In fact, an NCCN guideline suggests a minimum of 50 cc. In essence, if you can aspirate it by FNA, ideally getting 50 if not 100 cc, that's what you would make your diagnosis on. But no, 10 to 15 cc, that would be every patient.

DR. LEWIS: We need to close out this session in order to allow adequate time for the public comments, so I wish to thank all of the presenters and their response to questions. Thank you again for coming.

(Applause.)

DR. LEWIS: We'll now move to the second Open Public Hearing portion of this and

proceed with comments in the same manner as we did this morning. Commander Garcia will read the Public Hearing disclosure statement prior to calling on the individual presenters.

CDR GARCIA: Thank you, Dr. Lewis.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it's important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you, Dr. Lewis.

DR. LEWIS: We'll now begin the public comment, and the rules apply the same as this morning. You have the indicator light in front of you. Green carries you up to 2 minutes and 45 seconds, orange to 3 minutes, and red thereafter. We sincerely ask all of you to limit your comments to 3 minutes in order to give all of the later speakers time to have their opportunity. We have strictly 1 hour set aside for this and 21 speakers, and so we need to adhere to those limits quite strictly.

We'll begin with Kristi Evans.

MS. EVANS: My name is Kristi Evans, and I am from Fort Worth, Texas. I am

speaking on behalf of myself, a patient with breast implants. I am representing the powerfully positive option of breast implants for women needing reconstruction.

Eight years ago, I was diagnosed with invasive breast cancer. I had a bilateral mastectomy with reconstruction using smooth round silicone implants, Allergan Style 45. I have had absolutely no problems at all stemming from or with my implants. I cannot even begin to imagine not having this option to restore what breast cancer destroyed and took from me.

I will be forever grateful to my plastic surgeon who explained my options fully and helped me to make an informed choice about breast implants. My plastic surgeon still sees me regularly and has advised me about implant monitoring with MRI. I cannot afford to have an MRI every 2 years and would love for there to be a less expensive protocol established that I could follow.

I currently work at a large hospital system in Texas as a breast cancer patient navigator. I left my job as a public educator 8 years ago to help women navigate the overwhelming world of breast cancer. Breast reconstruction is one of the main areas that patients have so many questions and concerns about. Over the past 7 years in my position, I have seen the lives of thousands of women positively affected by the option of breast implants. Women need and want to have options, and I believe implants are an extremely invaluable and safe option.

While I have seen patients return to my hospital for known complications of breast implants, such as infection and capsular contracture, I have not personally seen one patient return to the hospital with a diagnosis of BIA-ALCL or complaints of systemic issues resulting from their implants.

What we as patients desperately need is a reliable, reputable place to turn to that has scientific evidence-based data concerning implants, so that each and every woman can

make the best-informed decision for herself. We need good evidence on the safety of breast implants and monitoring protocols. And social media is not the place to research healthcare options.

In conclusion, personally and professionally, I feel that implants are safe and must remain an option for reconstruction after breast cancer.

DR. LEWIS: Thank you very much.

Next is Dr. Barry Fernando.

DR. FERNANDO: Hi, my name is Dr. Barry Fernando. I'm a board-certified plastic surgeon who has been in practice for 31 years. I'm also the CEO of Anzu, a technology company specializing in data analytics and collaborative physician-patient platforms.

The problem today is that we have significant barriers with manual data entry and incompatible electronic medical record systems. With the Aesthetic Society, we have developed a novel, advanced, seamless data collection platform called the Aesthetic Neural Network, or ANN, which addresses current shortcomings in data entry and facilitates data on long-term longitudinal breast implant research. This novel mobile app technology will be the world's largest aesthetic surgery database and will share relevant breast implant data with the National Breast Implant Registry.

The Aesthetic Neural Network, or ANN, was launched in May of 2017 for members of the Aesthetic Society to share unidentified practice management data that is automatically extracted. Phase 1 requires no second data entry, and it's automatically collected and standardized and is compatible with most electronic medical record systems. On an average, we collect between 1,200 and 1,500 new procedures a day. All automatically extracted patient data in ANN is anonymized and de-identified, adhering to HIPAA Safe Harbor guidelines. The growth has been substantial since May of 2017, now encompassing over 730,000 patients and including 183,000 breast implant procedures.

ANN Phase 2 was launched in January of 2019, integrating mobile app technology. The system was built to solve the known barrier of manual data entry by leveraging mobile technology to provide frictionless data collection. Other features include security through biometric validation and a built-in scanning technology for automatic implant registration at the time of surgery.

Phase 3 is what we call real-time point-of-service interface based on a practice calendar. If we had access to practice calendar events, it simplifies many complex interactions, including physician data entry forms, patient survey forms, real-time access to educational information, and the ability to join a clinical study or activate a patient within a study or a survey.

The ANN interface will provide a novel solution for long-term breast implant tracking and surveillance that has not previously existed. The ANN engine will revolutionize data collection. This will facilitate patient engagement through a mobile app, allow electronic collaboration between patients and surgeons, provide secure central data collection for ongoing and future breast implant studies, and it will share the relevant data with the National Breast Implant Registry.

Thank you very much.

(Applause.)

DR. LEWIS: Ms. Michelle Forney.

MS. FORNEY: Hi, there. Thank you for your time today. My name is Michelle Forney. I traveled here from California on my own expense. I had McGhan Allergan Biocell textured implants. I am also a global patient advocate and have seen real-time concerns not only during my own journey but see women struggling every day to get tested for BIA-ALCL.

I had my breast implants for 19 years. I never knew about BIA-ALCL until 3 years into

symptoms, and I was diagnosed in 2018. My symptoms started in January 2015 when I had asymmetry, swelling, pain, and an intense itching in the right breast. They lasted through December 2017, and I displayed many symptoms of BIA-ALCL. I relentlessly saw OB/GYNs, dermatologists, family physicians, and even my plastic surgeon that implanted me, as well as multiple mammograms and an ultrasound. Still, at no time BIA-ALCL was mentioned to me. My symptoms were dismissed as other underlying issues.

In December 2017, my breast swelled over double the size. I again met with three more physicians and no mention of it. However, another ultrasound and mammogram were performed, and an effusion was noted.

Then finally, on December 28th, 2017, I learned about this cancer. I immediately consulted with a breast surgeon who performed a fine needle aspiration to rule out lymphoma. However, negligently, my pathology came back negative for lymphoma, and I was referred to plastic surgery. I met with a plastic surgeon, Dr. Brian Parrett at CPMC in San Francisco, and he recommended a capsulectomy and tissue testing. I had the surgery and my tissue tests came back as positive for BIA-ALCL.

At that time Dr. Parrett spoke to me about my next steps for oncology. I was Stage IIa. After further review of my fluid test, we found than an error was made at the pathology lab. Although 120 mL of fluid were aspirated, only 10 mL were tested. As you heard from Dr. Clemens today, you need 50 mL. We are seeing this pathology error made over and over again, against the NCCN guidelines. In fact, 9% of the diagnosed women in our Facebook group have had this same error. This is negligent.

If I would not have made the decision to not have my capsulectomy, I would not possibly be alive today or at the late stages of ALCL. My oncology journey has started at MD Anderson.

It took me 3 years, over nine doctor appointments, four mammograms, two

ultrasounds, a fine needle aspiration, and finally, a surgery to get me diagnosed with this cancer, this manmade cancer.

This is my beloved pet, Stella. She just passed away last Sunday due to lymphoma. It took her veterinarian 4 hours to diagnose her from her onset of symptoms. What does this tell you?

I urge you to consider the call to actions that we have presented to you and, most importantly, remove these textured implants from the market. They're a manmade cancer. And add a patient representative on the breast implant advisory team. We need to ensure that women's health and safety is taken care of.

Thank you.

(Applause.)

DR. LEWIS: Thank you.

Ms. Nancy Gallegos.

MS. GALLEGOS: I'm sorry, I'm a little emotional because I still have implants and I'm very sick. Thank you for allowing me the chance to share my story with your respected panel. My name is Nancy Gallegos. I traveled from Fresno, California, on my own expense, so I have no conflict of interest.

I decided at the age of 24 to get my breast implants. I was young, very vulnerable, and just knew this would change my confidence for the better. Self-esteem was all I wanted. So, I was implanted with Allergan textured saline implants. I might add, I still feel very sick today. One would say that you look just fine. This is just a mask. Internally, I am suffering.

My health issues started 6 years ago. For many years I lived symptom free until things came crashing down in 2013. The once up-beat, motivated, very confident woman had turned into a woman who could not get off of her couch, drive her daughter to school,

or pass a mandatory test on her job in order to stay employed. My husband used to describe me as independent, motivated, and extremely outgoing. Anyone who has known me would say the same. Now he sadly feels this illness has consumed my life. My illness is all I talk about, and he would like the old me to come back. Even though he supports me, I know I'm not the same person he married 10 years ago.

Today I'm asking for proper informed consent. I feel we should be provided the very crucial information, and at that point, the patient can make their own decision whether they would like to proceed.

One thing I might add is it's very difficult going to your physicians because we are so ill and they have no idea what breast implant illness is. Therefore, many incorrect diagnoses are given with medication prescribed that has no effect. I, myself, deal with depression, weight gain, joint pain, insomnia, autoimmune disease, vitamin D deficiency, anemia, high blood pressure, memory loss, and much, much more.

I am so thankful a friend directed me to the breast implant illness page. And thank you for that, social media, for helping me out. I now feel I belong somewhere. These women are dealing with the same issues I have been crying about for years. This page has given me an insight as to what no doctor has ever been able to explain or diagnose. I am a woman in my 40s that has to carry around a pillbox everywhere I go, numerous medications with no ultimate effect.

I cannot wait to explant; however, the cost to remove my implants cost me almost double what I paid to get them put in. Health insurance makes it near impossible to cover. Why do I pay thousands of dollars into an expensive PPO insurance, yet I get denied coverage for explant when I'm extremely ill? I just want my health back.

In closing, I ask you today to please listen and know we are women in a world of struggle. I would hope that if you had a wife, child, or family member crying out for your

help and they too have breast implants, please listen and know these implants are making women deathly ill and changing our lives entirely.

Thank you.

DR. LEWIS: Thank you.

(Applause.)

DR. LEWIS: Dr. Danielle DeLuca-Pytell.

DR. DeLUCA-PYTELL: Good afternoon. I'm Dr. Danielle DeLuca-Pytell. I have been a board-certified plastic surgeon for 14 years. I would like to share my experience of how I educate my patients desiring breast implants.

After taking a complete medical history, I review the history of breast implants and the controversies which led to the silicone implant moratorium in the 1990s. We discussed how those studies were done, and that after analyzing the data, it was not a statistical significance to having breast implants and systemic disease. We discuss that while some women may develop autoimmune or connective tissue disease, we do not have a causal relationship with breast implants.

We specifically discuss BIA-ALCL. We discuss that this disease appears to be related to the surface texture of the breast implants, not the material with which they are filled. While at this time we have only confirmed cases with textured implants, we are still worried about this disease, so I discuss BIA-ALCL with everyone. I explain that it is a rare disease with a late onset presentation. We discuss that it can be cured if detected early. Here I stress the importance of regular yearly follow-up with their plastic surgeon. Other physicians may be unfamiliar with appropriate testing which could result in a delayed diagnosis.

For my reconstructive patients, this is easier to reinforce. My younger, healthy, and happy patients may not be used to the idea of regular well checkups. I encourage this for

implant checks and breast exams. There is never a charge for this follow-up.

We also discuss that implants are not lifetime devices. I clearly tell them to expect another operation in the future. This could be due to a local complication such as rupture, contracture, or a displacement or for personal preference. We discuss implant monitoring for rupture. We discuss silent rupture is common with silicone gel-filled implants and that radiographic surveillance is needed for diagnosis of rupture. We discuss the FDA recommendation for MRI. In the first 10 years when rupture rates are low, I think it is unreasonable to recommend frequent MRI screens, which are costly. As the implant manufacturer I use offers financial assistance for surgical expenses, I do recommend looking with MRI before that warranty expires.

This is a Pandora's box, though. I have patients with known capsular contracture and known ruptures that opt to avoid surgery for various reasons. If a silent rupture has caused no harm, do we need to operate? This is a conversation that must be individualized, again stressing the importance of routine follow-up.

Finally, despite the rare but present association between BIA-ALCL and textured breast implants, I believe that women should have the right to choose. For my reconstructive patients, anatomically shaped silicone gel implants have been one of the best cosmetic advances I have seen since entering practice. I think of my patient who says you gave me my life back. We should continue to study this powerful reconstructive device to ensure the best options and outcomes for all patients.

Thank you.

DR. LEWIS: Thank you.

Ms. Sybil Goldrich.

MS. GOLDRICH: Good afternoon, my name is Sybil Niden Goldrich, and I have been, since 1988, an advocate for women's health regarding breast implants. I currently serve on

the claimants' advisory committee of the Dow Corning bankruptcy and was a member of the negotiating team of MDL 926, the litigation that covered all implants except those of Dow Corning. I am not a lawyer. I serve on those committees at the request of Federal District Court Judge Sam C. Pointer and Denise Page Hood in Michigan. Sam C. Pointer is deceased.

After writing an article for *Ms.* magazine about my own horrific experience with leaking breast implants following bilateral mastectomy, the FDA -- I thank you, FDA. They asked me to come and speak at an Advisory Committee in 1988. During that meeting, Dr. Sid Wolfe of Public Citizen testified that smooth cell carcinoma had been documented in silicone implants in laboratory animals. And now 30 years later we're discussing anaplastic large cell lymphoma caused by implants in humans. I just find that a little bit of a disconnect. I also heard today that renal cell carcinoma may be involved. I have had renal cell carcinoma.

Breast implants were invented in the early '60s and have been available to patients for close to 50, 60 years, and we're still arguing about their safety. I find that unacceptable and astonishing.

Well over 500,000 women applied for benefits in MDL 926, the litigation that covered injuries to claimants caused by all manufacturers except for Dow Corning. Thousands more claimants came forward with the Dow Corning bankruptcy. The injuries claimed and ultimately covered by the funds in the litigation are those that are still documented in the manufacturers' current package insert. The manufacturers agreed to compensate claimants for their injuries, which acknowledges that the manufacturers clearly understood that the claims were valid.

Over $3 billion in compensation, and that does not include the overhead to distribute $3 billion, has been paid to injured women, and they are not yet done. However, these women were not only physically injured but also had to deal with being accused by

the breast implant companies, plastic surgeons, and the media as being greedy. I know what these women have gone through, and I assure you, that's not the case. In fact, payments made to these women were barely enough to cover their medical expenses.

In 2006 the FDA approved silicone gel breast implants made by two companies. The approval was contingent on two 10-year studies of 40,000 women each. But the companies lost track of most of the patients, making those studies useless. You know, if I didn't come in with my homework, I'd be in trouble, and if the FDA doesn't have a financial arm to fine people, there should be a big ad in the newspaper: Delinquent.

My last remark: I'm asking you to understand the sense of the urgency felt by all the women who have traveled here today. We are asking that you demand the manufacturers fulfill the requirements that you set forth when approving breast implants and that have been blatantly ignored.

Thank you.

(Applause.)

DR. LEWIS: Ms. Gretchen Goodell.

MS. GOODELL: I want to thank the Panel for allowing me to speak today. My name is Gretchen Goodell Bridge, and I'm a woman's health nurse practitioner and Air Force veteran from Phoenix, Arizona. I am also a patient whose health was severely compromised by intact saline implants. I got them in 2004 and felt fully confident that they were safe.

Over the next 14 years I attributed all of my newly developing health issues to stress until 2016 when I started losing feeling in my arms and hands. My brain MRI showed nonspecific white inflammatory lesions, all of my brain, that looked like MS but they weren't MS. The source of the lesions was a mystery.

Fast forward to 2018, and my symptoms were all worsening. Even as a provider myself, I couldn't make sense of what was happening with me until a friend posted on

Facebook that she was having her implants removed because they were making her sick. For about 10 seconds I thought she was crazy, until I read her symptoms, and I was stunned. It was like reading my own medical record. It shouldn't take a chance viewing on Facebook for a woman to be informed of what is causing her significant health problems. Women don't go back to their plastic surgeons when they're sick; they go to the neurologist, the cardiologist, the dermatologist, like I did. Frankly, if I had a patient come to me a year ago and say Gretchen, you know, I'm losing a bunch of hair and I keep getting these weird rashes, I think it could be because of my implants, I likely would've dismissed the idea because I literally had never heard of such a thing until I realized it was happening to me.

My goal is to educate all healthcare providers that simply having breast implants needs to be considered a risk factor for women who suffer from all the symptoms that implants can cause. When an otherwise healthy 27-year-old presents to a rheumatologist with new onset generalized aching in all her joints, you might discuss with her that of course we will look into all causes, but yes, having breast implants can do that.

I respectfully implore the FDA to put out a Dear Healthcare Provider letter and give breast implant illness a name. Please educate all providers on the autoimmune symptoms that implants can cause. Such a letter should state that the way to alleviate the symptoms is to have the implants and the capsule removed. This needs to be common knowledge in the entire medical community. Patients and their providers need to understand that it is imperative that the capsule, not just the implant, also be removed in sick women because the capsule itself can cause an ongoing systemic inflammatory response.

I disagree with the notion that more long-term studies need to be completed on the safety of breast implants and instead encourage retrospective studies. Thousands of sick women, including myself, have already been the guinea pigs for the implant manufacturers. And we are the proof that breast implants are not safe. Thank you so much for listening.

(Applause.)

DR. LEWIS: Thank you.

Dr. Ashley Gordon.

DR. GORDON: My name is Ashley Gordon, and I'm a board-certified plastic surgeon who's been in practice for 13 years. I'm also a breast implant patient for 17 years with smooth silicone gel implants. I have not had any issues with my implants and still experience the positive benefits of them. I'm a member of the Aesthetic Society, and a large portion of my practice focuses solely on aesthetic enhancement of the breast. I have personally placed close to 10,000 devices, and I follow my patients' long-term results.

Breast implants have a positive benefit-risk based on known scientific data and from my clinical and personal experience. Revisionary breast surgery comprises approximately 20% of my practice. In the majority of revisionary cases, I utilize P4HB resorbable natural scaffold for soft tissue support to better help maintain the patient's breast shape and position on the chest wall. You're going to hear more about P4HB tomorrow, but I was only able to come today.

P4HB has been used in three to four million patients, and mesh scaffolds have been used in over 100,000 patients with excellent outcomes and low adverse events. I'm also using it more frequently in primary cases where the patient has poor skin quality and is at high risk for recurrent ptosis. My short- and long-term experience with this product has confirmed that patients will have a longer-lasting result with the stabilized breast shape and position compared with patients that do not have this support. I believe that using soft tissue support in these patients has few complications, and when they do occur, they can be easily managed. P4HB is an important tool in minimizing reoperation in these patients and breaking the breast revision cycle.

Excellent post-approval clinical studies have been published on P4HB in breast

reduction and mastopexies that mirror my clinical experience with these products, and I support continued independent research that gathers post-approval, patient-centric, and implant-specific long-term data so as to better understand benefit-risk.

With regard to breast implant illness, we are committed, as a society, to understand what the association is in these patients who have these symptoms, whether individuals have a genetic predisposition to having an adverse immunologic response and the workup that is required before and after implant removal.

I look forward to the results from the data-driven research studies that are starting soon by the Aesthetic Society's research arm, ASERF. And since my inception in practice, I have tracked my own complications from my cases, and since 2018 I have entered every implant case with the National Breast Implant Registry. The Aesthetic Society and the Aesthetic Neural Network technology (ANN) will share valuable data to this national registry, and this will be invaluable in helping us answer future questions on breast medical devices.

Thank you for your time.

DR. LEWIS: Thank you.

Dr. Chelsea Hagopian.

DR. HAGOPIAN: Good afternoon and thank you for the opportunity to speak today. My name is Chelsea Hagopian. I am a nurse practitioner working in plastic and reconstructive surgery, and I hold a doctorate of nursing practice and health systems leadership. My goal today is to present the nursing perspective on how certified patient decision aids can be used to directly support informed consent discussions between patients and surgeons.

Certified patient decision aids are structured, evidence-based educational tools. Standards for certification are published by the International Patient Decision Aids

Standards Collaboration and endorsed by the National Quality Forum. The specific relevance to this Panel is that use of these tools could help connect breast implant safety, effectiveness, and real-world evidence to patients in a meaningful way.

The decision to have breast implant surgery, whether for cosmetic or reconstructive purposes, is preference sensitive. More than one medically appropriate treatment option is available, so the patient's informed preferences are required to guide decision making. Here, best practice to accomplish effective informed consent is through a process of shared decision making.

Surgeons use data-driven evidence and their clinical expertise to educate patients of treatment options and associated risks and benefits. Patients use the knowledge of their own experiences to inform surgeons of their values and informed preferences.

Informed consent discussions do not occur in a vacuum. Patients have varying levels of understanding of their surgical options and therapeutic goals. Readily available patient education materials and lengthy informed consent documents are often not helpful. As an alternative to traditional informed consent materials, certified patient decision aids can empower the patient and each member of the care team with quality and understandable information. These tools better support collaborative informed consent discussions between patients and their surgeons by reinforcing key data points that can be updated as new information is discovered.

No certified patient decision aid exists for aesthetic procedures. For that reason, I designed a development process model for creating certifiable patient decision aids to potentially replace traditional informed consent documents for aesthetic procedures. Presently, I'm working with the Aesthetic Society to complete a pilot study focused on primary breast augmentation. This work aligns with existing efforts of the FDA to ensure that patients are better informed about the risks of breast implants both at the time of

breast implant surgery and longitudinally.

I encourage the Panel and the FDA to consider the potential value of using certified patient decision aids to communicate breast implant safety, effectiveness, and real-world evidence to patients to better support best practice for informed consent discussions between patients and surgeons.

Thank you.

DR. LEWIS: Thank you.

Dr. Melinda Haws.

DR. HAWS: Good afternoon. My name is Dr. Melinda Haws. I'm a board-certified plastic surgeon. I've been in practice for 21 years. I also am a breast augmentation patient with textured breast implants that have been in place for about 21 years. I'm a member of the Aesthetic Society, and I'm here as the Chair of the BII Task Force that the Aesthetic Society has started. We formed this in response to an increase in the number of the breast implant illness patients that were being seen in all of our offices.

To obtain quick information, the task force distributed surveys to our members, and what we found was it wasn't just me, it wasn't just him; half of our members are seeing breast implant illness patients. So, we dug a little deeper. We found most of these women are between the age of 35 to 55, and we found implant removal, once performed, highly variable regression of the symptoms; they were kind of all over the place. But this is retrospective data, this is not great data, so we're starting more studies, and we want you all to help us with those.

The Aesthetic Society's research arm, ASERF, has designed two studies looking at the breast implant patients and their symptoms. These are novel studies looking at them through bacterial as well as genetic origins. Patients with breast implants or electing to have breast implants deserve accurate, credible, up-to-date information. Previous studies

are no comfort to the many intelligent, articulate women here who complain of these symptoms and are suffering. Breast implants are a 100% elective device, and women are well within their rights to get these removed at any time. But we need accurate data for informed consent, and that's why the ASERF studies are important.

The Aesthetic Society task force has also developed talking points so that I can help these women be respected and heard when they go to plastic surgeons' offices. We need to educate our members like you've educated your members. We want to reinforce the physician-patient relationship again. We want to make sure the patient is respected and heard. We're also looking at pre- and post-surgery questionnaires, and I ask you to please follow up with your plastic surgeons so we can see what symptoms resolve and when, so that when I see a new patient I can say 30% likelihood, 75% likelihood this will go away.

All of this data is going to be fed into the Aesthetic Neural Network, the Aesthetic Society's arm, so that we can then add that data to the National Breast Implant Registry when it's needed.

So, going forward, the Aesthetic Society's BII talking points, the questionnaires and the data collection, we want to bridge the gap between physicians and patients, we want to work together to investigate these symptoms, and as medicine continues to evolve, we want to be advocates for you and for our future patients.

Thank you.

(Applause.)

DR. LEWIS: Ms. Raylene Hollrah.

MS. HOLLRAH: Hi, my name is Raylene Hollrah, and I traveled from Missouri on my own expense, and I have no conflict of interest.

I was diagnosed with breast cancer at the age of 33. I had a bilateral mastectomy without immediate reconstruction followed by chemotherapy. After the following year of

treatment, I was very concerned about not having a chest and I was struggling. I went to three different plastic surgeons for consult on my reconstruction options. All three were united, and it was a safe choice to use textured implants as a reconstruction.

Upon this, I was part of the 10-year mandated study to follow my reconstruction path. Ironically, I was dropped from that study at the same time I was diagnosed with my second cancer, with no reason or notification why. I was diagnosed with BIA-ALCL on June 21st, 2013. Yes, a manmade cancer from my breast implants. I was never warned, I was never notified of the risk, and my life was forever changed again from another cancer diagnosis. When I was diagnosed, I picked up my whole life and moved to Houston, Texas, MD Anderson.

On there, you can see in 2018 Allergan came out with the ConfidencePlus warranty program. They'll pay up to a thousand dollars for diagnostic testing and up to 7,500 for out-of-pocket surgical costs. My costs to date at MD Anderson since my diagnosis is $288,133.50. That does not include my lost time working, traveling, or lodging, and I never had to have chemotherapy because of my ALCL. That number would be a lot higher.

I also stand here today in honor of my daughter. She's 15 years old, and when she turns 18, she will be tested for the BRCA mutation. She couldn't be here today because I said studies come first and she should be at school right now. But in this letter to the FDA, she talks about how thankful she is to be here. Memories, her prom, her first one's coming up, I'm going to be there to help her get ready, take photos, and I know I'll cry. But at the end she says, "My mom is one of the lucky ones, and I was wondering if you're willing to admit that you could've taken this all away from me. Are you willing to keep these cancer-causing implants on the market and put other kids' mothers at risk?"

This is the fourth time today that I'm testifying before the FDA in the past couple years. Thank you for taking the time to listen, but I've been clear and concise every time

I've come. We need mandated patient informed consent, we need a mandated black box warning, we need a mandated patient checklist, and most importantly, 19 women have died. You have the power and the authority to remove this cancer-causing implant from the market.

Thank you.

(Applause.)

DR. LEWIS: Thank you.

Ms. Tara Hopko.

MS. HOPKO: Hi. Sorry, I wasn't expecting to be called up here today. Okay. My name is Tara Hopko, and I traveled here from New Jersey at my own expense. I have no conflict of interest being here. Thank you for letting me share my story with you. I'm very happy to be here because 1 year ago I truly did not know that I would be alive today.

At age 35 I was a wife, a mom, a former body builder. I was energetic, happy and healthy, athletic. I decided to have a breast augmentation for aesthetic reasons. I wanted to feel more like a woman.

My symptoms began subtly but almost immediately. Just weeks after my surgery, I become uncharacteristically exhausted. Most nights I was asleep before my two young children. They'd have to wake me on the couch to tuck them in bed. My lymph nodes were swollen throughout my body, and I had horrible brain fog to the point where I had to carry a notebook at work to write down people's names just to remember them. I had panic attacks that woke me in the night and anxiety that kept me shut in, in my house. The difficulty breathing and the heart palpitations made it impossible to exercise anymore. My hair stopped growing, my vision was blurry. Due to the silent reflux, all the GI issues, I couldn't eat without pain and nausea.

Every morning getting out of bed, my legs were numb and my feet burned. My joints

ached constantly, and I ended up in the hospital on Christmas Day 2017. I was unable to walk. They didn't know why. Spontaneous tendons and -- spontaneous tears in my tendons. It was debilitating. My worse symptom was my acne. Most nights I would sit with icepacks on my face. I had cystic acne. I don't know if you can see this picture, I wasn't prepared to be up here, but I was in so much pain all the time.

At the point where I thought I was so sick, I spoke with my husband and I talked to him about my wishes for when I die. I was prepared to say goodbye to my family because I didn't think that I was going to make it through all of this. Doctors told me that I was simply a busy working mom going through early menopause. My frustration led me to search the internet because, unfortunately, social media is the only place that we can turn sometimes. These doctors suggested yoga, meditation, antidepressants. I had my implants taken out almost a year ago. My acne is gone. My symptoms are almost all gone. I am the person that I used to be. And if I knew anything of what could have happened, I would've said no thank you to my implants.

I implore you, please take textured implants off of the market, and I implore you to please give informed consent to these women. We deserve to know. Everyone deserves to have a choice, I agree with that, but we deserve to have an informed choice.

Thank you so much.

(Applause.)

DR. LEWIS: Meredith Kilmer.

MS. KILMER: My name is Meredith Kilmer from Raleigh, North Carolina, and I thank you for your attention. I had Mentor saline textured implants for 11 years. I am a patient and a caretaker. I implanted in 2001 and explanted in 2012. I never received a booklet or was told that they would need to be replaced. I was told they were safe, FDA approved, and would outlive me in my grave. I suffered debilitating neurological and systemic

symptoms, fibromyalgia, brain fog, fatigue, joint pain, skin rashes. However, I have come to tell you about my children.

I have four kids, two born before breast implants and two children conceived while I had breast implants. My children born before breast implants have never had pneumonia, chronic bronchitis, allergies, or morning stiffness. My younger children struggle with the same atypical health problems that I had. When my daughter Paige was born, her first antibiotic and antifungal was given at just 3 weeks of age. She was chronically ill, had numerous pneumonias and skin rashes. Ava is much more symptomatic. By age 3, she had 13 antibiotics with multiple antifungals, steroids, esophageal issues, and is chronically not well. Her quality of life is a struggle. She has fibromyalgia symptoms, chronic neck and fascia stiffness, skin rashes, and she's exhausted most of every day. Both girls have bone and joint pain, and their pediatricians state that breast implant illness and its symptoms are not recognized in the medical journals of health disorders. The out-of-pocket healthcare cost for myself and my daughters are substantial, and my children are not the only kids with these symptoms whose mother had breast implants.

In light of this FDA review, I reached out to women who had had children while implanted, and within the first 24 hours I received 207 written responses from mothers totaling 285 symptomatic children just like my girls. Like me, many of these mothers have non-symptomatic healthy children born before breast implants.

FDA, I urge you to consider the five following points to ensure the health and safety of women and their children.

We need an alert system to pediatricians and a registry run by pediatricians gathering information on symptomatic children born from mothers with breast implants.

The FDA should require an updated study on the amount of cyclic siloxanes and other chemicals found in the breast milk of lactating moms and the breast implant

chemicals that are affecting our babies.

It is imperative we have a study to determine the safety of breast implant chemicals and its heavy metals crossing through the placental wall and passed through breast milk.

We must have better informed consent to replace the lengthy technical manufacturers' brochures so the patients can determine the risks are low enough to implant or not.

And we need the medical community and pediatricians to recognize that breast implants can be harmful not only to the mothers but to their precious children in utero.

Thank you.

(Applause.)

DR. LEWIS: Thank you.

Dr. Clare Lee.

(No response.)

DR. LEWIS: Okay. David Sieber.

DR. SIEBER: My name is David Sieber, and I'm a board-certified plastic surgeon in private practice in San Francisco. I have no financial disclosures.

I'm the Chair of the Grant Committee for the Aesthetic Surgery Education and Research Foundation, and I serve as a peer reviewer for the *Aesthetic Surgery Journal* and the *Journal of Plastic and Reconstructive Surgery*. I perform only cosmetic breast implant surgery, which makes up approximately 40% of my surgical practice.

The FDA has asked you to discuss MRI screening recommendations for silicone breast implant silent rupture and whether these recommendations should be changed. Screening is very important; however, many women are not compliant with the current recommendations. I am here to advocate an alternative screening method, high-resolution ultrasound, which we believe will result in greater compliance and subsequent clinical

benefit.

There are approximately 300,000 women who undergo breast augmentation surgery in the United States annually. Based on the June 2011 guidance document, the FDA currently recommends that women with silicone implants get their first breast MRI 3 years after they receive the implants and every 2 years thereafter to detect silent ruptures. This recommendation is based on core studies in which MRI was used to detect implant rupture and to assess implant shell integrity.

In August of 2011, an FDA Advisory Panel noted the current scientific data and recommendations for MRI screening for silent rupture and questioned whether much was gained by this recommendation. There was a concern expressed about cost to patients and mentioned false positive findings and whether information about silent rupture would change practice, such as decisions about removal of the device.

In my clinical experience, despite the recommendations by the manufacturers and the FDA, patients are not having the MRIs performed for a variety of reasons. The most common reason is cost. Since much of my practice is cosmetic augmentations, an MRI is often not covered by insurance carriers, with the average out-of-pocket costs of approximately $2,600 per MRI. Over the course of 10 years, patients would be spending over $10,000 in order to follow the current FDA recommendations.

In a paper cited in the FDA update on silicone implants, written by Gorczyca, there's very little attention paid to valid alternatives to MRI, such as high-resolution ultrasound. A paper published by Bengston in 2012 demonstrated that evaluation of implant shell integrity was able to easily be learned and performed using an in-office based ultrasound. An additional paper published in 2017 by myself and Adams also confirmed in-office ultrasound could easily and effectively be implemented to follow breast implants, as well as identify gel implant shell failure.

So why then are we recommending to our patients a test which is often cost prohibitive and has a very low compliance rate? In my professional experience, high-resolution ultrasound may act as a better screening alternative to MRI due to its accessibility, which may lead to a higher patient compliance.

Thank you for your time today.

(Applause.)

DR. LEWIS: Thank you.

Ms. Kim Platt.

MS. PLATT: Good afternoon. My name is Kimberly Platt, and I'm here from Cleveland, Ohio. I have no disclosures. I'm here to speak about my diagnosis of breast implant-associated anaplastic large cell lymphoma, also known as cancer.

My journey begins in December of 2004 after consenting to take part in a 10-year research study for McGhan 410 textured implants that required adherence to specific guidelines for follow-up, which I did for the next 7 years. In 2011 I was informed the 410 research study was terminated.

In 2013 I began to notice changes in my right breast, which included increasing in size and pain of unknown origin. After meeting with my plastic surgeon, I had a mammogram, an ultrasound-guided aspiration of clear yellow fluid, a breast MRI, and consultations by both a breast and a plastic surgeon. This was my first education on this cancer.

Each time I was aspirated over the next 2½-year period, it remained negative for malignant cells. We decided to watch.

Finally, in December of 2017, I had a 90% capsulectomy on the right side due to the capsule position, a bilateral implant removal with implant exchange. Remember, my fluid was negative. During my follow-up appointment, I was informed I was positive for BIA-ALCL

and was scheduled for a second surgery the following week.

In January 2011 FDA issued its first communication on the findings of this cancer. In 2013 both Allergan and Mentor gained FDA approval for the textured implants. Meanwhile I am entering early stages of right breast changes, which should have been my ninth year of surveillance for the terminated 10-year research study.

With this emerging disease, the amount of research and published articles since my diagnosis in 2017 proves to me that my cancer may not be as rare as once stated, that BIA-ALCL is like being struck by lightning. When conducting a PubMed literature search from January of this year, there have been 28 articles published in just 3 months. Is this cancer as rare as once thought?

My purpose and goal here today is to inform the Panel of my personal journey to gain education and to collaborate with the FDA Advisory Panel by supporting the removal of textured implants from the market that has resulted in manmade lymphoma. I beg this advisory board, as I did with my plastic surgeon, to never use another textured implant. He has complied with my wish, and my healthcare organization has removed them from use as well. We must join Europe in banning textured implants. Plastic surgeons who do not have buy-in in this disease need to recognize the dangers for a select group of women. No one knows who we are.

It has been an honor and a privilege to speak to you today. Our paths would have never have crossed without this cancer. I would've preferred not to have crossed this path. What I have learned today is that Allergan is selling this information to this Committee that they had a robust follow-up with patients. I disagree. I am here to tell you that I was and will continue to be a willing part of research studies. Allergan left me. I didn't leave you.

(Applause.)

DR. LEWIS: Ms. Jennifer Harrington.

DR. HARRINGTON: Good afternoon. My name is Dr. Jennifer Harrington. I am a board-certified plastic surgeon from Minneapolis, Minnesota. I was involved in the largest FDA gel implant study in the country with Sientra.

I took my Hippocratic oath to be a physician back in 1994, and from that day, I really have tried to center my practice around always trying to do the right thing for my patients.

I've been asked to speak today on behalf of Sientra because I'm their medical director, but know that I have really no financial interest at all. I have brought myself here today. I'm a busy, busy plastic surgeon up in northern Minnesota, and I just kind of want to bring you a down-home approach to just kind of plastic surgery at large.

Plastic surgeons are really about trying to make people whole again. Whether we're putting a hand back on for a patient that's cut it off with an industrial trauma or a scalp back on from a little 6-year-old girl ripped off by a dog or a breast being put back on for a patient that had breast cancer, we really are about trying to do the right thing. I can tell you that in my practice of 19 years, I've cared for so many patients with so many issues regarding their breasts. Whether they're not the right size, they're too big, they're too small, they're wrong, they're asymmetric, or they don't have one or they've been radiated, it's a really big deal to not feel good about yourself. It causes back pain, neck pain, clothes don't fit right. And I frankly can't imagine living my life not feeling good about myself because when you feel good about yourself you live a great life and you do the right thing.

Life is about risks. We all take risks. That's what America is really all about. Well, we know about risks, we know that there's a greater risk for skin cancer, there's a greater risk for colon cancer, there's a greater risk for lung cancer, it's all out there. But our job really is to -- as we've heard from so many patients today with ALCL and BII, I want you guys to know we hear you, I hear you. We hear you. This has been very emotional. And we want you to know that, you know, we want to be your partner in this, and we want to be

informed, and we want to lead you to a very informed consent.

So, I plead to the Panel, you know, ALCL is real; we've heard about it. BII. I, like Dr. Haws, I take care of patients with BII also. Risk-benefit. I think putting in implants, by and large, is a great thing for patients. But I want you to know that I do think we need a more improved, you know, informed consent so that patients know exactly what they're getting themselves into.

I've very proud to be a member of our society. I can tell you that we have so many meetings, and we go to these meetings, and these rooms are frequently, you know, partially full. But whenever in the last 5 years there's been information about what is going on with BII-ALCL, I want everyone in this room to know that that room fills up like crazy and it's standing room only. We really care. One of the ways that I know that I would still continue to put breast implants back in patients is I always say to myself would I do it to my mom? Well, my mom's had breast cancer, my mom has a bilateral mastectomy, and I want you to know that today, with all that I know, I would put breast implants in my mom.

Thank you for your time.

(Applause.)

DR. LEWIS: Ms. Marie Jobson.

MS. JOBSON: Good afternoon. My name is Marie Jobson, and I'm from San Jose, California. I am here as a participant of Sientra's clinical trial program. I want to thank you so much for allowing me to speak, especially to speak on behalf of the men and women who will be receiving their cancer diagnoses, particularly the women who will have to make a tough decision on a double or single mastectomy in hopes of full reconstruction.

I was diagnosed with breast cancer in May of 2013 and after a lumpectomy was told I had unclear margins. That meant I still had cancer in my body. At that point I was filled with fear and anxiety in the weeks and months that followed as I faced my own mortality.

For me, my choice was to undergo a double mastectomy with full breast reconstruction. This was the best choice for me, as I had full faith and trust in a highly effective and qualified plastic surgeon and in partnership with the medical devices and textured implants that would be provided for me through my participation with Sientra's clinical trial.

These medical devices would provide safe, effective breast expanders and what I call very natural permanent breast prostheses, actually, as the implants would replace a very emotional body part that I was getting ready to lose. That decision was very emotional, as I had breastfed all four of my children.

As we all know, these medical devices are not a cure to cancer. At this point we don't have a cure for breast cancer. But what I do know is that it has been an integral part of my emotional, mental, and physical healing. My past experience with my breast cancer does not make me who I am and the success of my breast reconstruction, in partnership with a highly qualified plastic surgeon and the medical devices that were provided for me, has allowed me to live in the present moment. It has allowed me to live in the now. Whether it's wearing a bikini or having intimacy with my husband, I am able to live in the now and not be defined by my past experiences.

My hope is that the decision of the Committee will give the women, who will be undergoing their own breast cancer journey, the same opportunities and privileges that I was given during my breast cancer treatment.

Thank you very much.

DR. LEWIS: Thank you.

Ms. Maria Gmitro.

MS. GMITRO: Good afternoon. Thank you for the chance to speak today. My name is Maria Gmitro, and I traveled from South Carolina at my own expense to speak about my experience. In 2014 I had Mentor silicone breast implants placed to correct asymmetrical

breasts. I was healthy. My surgeon said they fixed all the issues from the '90s and that these were the new FDA-approved implants and were completely safe. I was never given a patient booklet. I loved my new implants. However, within 6 months I started developing strange symptoms, rashes, fatigue, digestive issues, brain fog, fibromyalgia, migraines. I had no idea they were related to my implants. I saw 10 different doctors, and not one of these specialists was able to determine the cause. I was prescribed countless medications and treatments, but nothing helped. My plastic surgeon only told me that my breasts looked great, but I felt awful. It was frustrating to be on so many treatment plans and living a healthy lifestyle but still be so sick. I ended up taking a leave of absence from my teaching job to focus on my health.

Facebook suggested a page to me called Breast Implant Illness and Healing by Nicole. As soon as I read the symptoms and the other women's experiences with BII, I knew I had to have my breast implants removed. When I went back to my surgeon, he threw his hands up at me, stating the FDA says there's no connection. I felt helpless.

My implants and scar capsules were removed in 2017, and almost immediately my joint pain, insomnia, and the constant feeling that I had a hangover was gone. My implants were not ruptured, and I'm gradually regaining my health, but I am scared about long-term damage. I only had my implants for 3 years.

I stand before you to tell you that if my doctors or I knew the symptoms to watch for, I could've explanted sooner, avoided years of illness and costly medical bills, had more quality time with my family, and my students would still have me as their teacher. I know firsthand how breast implants can impact a woman's health, and if I had known that the risks included debilitating breast implant illness or BIA-ALCL, I would have never chosen to have them placed into my body. The financial, physical, and emotional toll this has taken is devastating, and sadly, I am not alone because there are thousands of women with the

same story. Yes, I was happy with my implants until I became sick.

Respectfully, I implore you to require surgeons to provide informed consent including symptoms of BII and BIA-ALCL and issue the patient booklet. Inform all healthcare professionals of the symptoms of BII and BIA-ALCL. Provide a simple checklist to be signed by patients and their doctors and at least 1 week prior before getting implants to inform patients of the risks. Make no mistake, social media helped save my life.

Thank you for your time and consideration because no one should have to suffer the way we have. Thank you.

(Applause.)

DR. LEWIS: That concludes our public presentations this afternoon. Yes?

MS. BOWDEN: There were three cancellations --

DR. LEWIS: Turn the microphone on.

MS. BOWDEN: I was just wondering, there were three cancellations today, and I was supposed to speak. I was wondering if I could have that opportunity.

DR. LEWIS: Sorry, say again.

MS. BOWDEN: My name is Laura Bowden, and I'm on the cancellation list, and I know there were three people that didn't show up, so I was just wondering if I could have a chance to speak.

DR. LEWIS: Okay, please adhere to the 3 minutes.

MS. BOWDEN: I will. Thank you. My name is Laura Bowden. I have not been paid to speak here today. I had Dow Corning breast implants in 1990, removed in '92, fell severely ill 4 months after they were put in, almost 2 years of trying to figure out why I was so sick. By the grace of God, I had a full recovery upon removal. Cause and effect at its best. I could give more details regarding my illness, but it seems these amazingly strong and well-educated women that I'm honored here to stand with today have that part

covered. I'm here to talk about history. See, I believe I'm watching history repeat itself.

When I removed my implants in 1992 and regained my health, regained my health overnight, I may add, it lit a fire under me. I vowed to speak for all those sick women I was blessed to meet at Baylor University, where my implants were removed, speaking for those that had no voice, an underground of sick women, all with the same symptoms. Coincidence? I think not.

I am one of the lucky ones. I became fierce in this fight to end this travesty back then, taking on the CEO for Dow Corning on Oprah with other brave women, spoke loud whenever I had the chance. Jennie Jones mainstream news, picketing in Chicago, spoke with Ralph Nader. Fires that were started only to be put out by a much more powerful force, Dow Corning. The FDA made a poor attempt at the moratorium to pull these devices off the market, only to be lifted and put back on the market in 2006. No new improved, no better safety studies. All for the financial gain within a greedy industry. Inexcusable.

And now, here I find myself surrounded by a second generation of sick women, thousands and thousands of sick women. Mothers, grandmothers, sisters, and daughters whose lives have been destroyed once again. How have we found ourselves here again? Did we not learn back in the '90s about the dangers of breast implants? Were we not listening? Did you not see the devastation of so many innocent lives? I heard them all. I heard their cries and felt their pain. I was one of them at one time. Not until I met my dear friend Latasha 6 months ago did I realize nothing has changed. Thousands of sick women. Doctors in denial, no insurance coverage. Struggling to get a diagnosis. Nothing has changed. It is beyond deplorable that this is still going on. I attended conferences of so many brave doctors who were doing the studies back then, concluding that yes, silicone adjuvant breast disease was the correct diagnosis. Sadly, they were few and far between willing to admit it. Nothing has changed. Except now we have evidence of a real form of

cancer every breast implant causes: BIA-ALCL. I can't help but remember while attending one of the conferences an immunologist spoke. I will never forget his words. Women will develop rare forms of cancer from these faulty devices down the road. Mark my words. He knew. He knew the devastation that these faulty devices would fall onto these innocent women. It is not as if this is a new illness. You know it, I know it, and every courageous woman in this room knows it.

I beg you, I urge you, to do what is right to ensure that another generation never has to fall under such pain and isolation. So many sick women have traveled from afar to speak here only to have their voices heard to make a difference. I am beyond honored to stand with these strong and resilient women to see that this never happens again. You have the power to make that happen. Please do what is right.

Thank you for allowing me to speak.

(Applause.)

DR. LEWIS: We wish to thank all of the people who have come to speak and acknowledge their contributions. The Panel realizes how difficult it is for you to travel here at your own expense and share these personal stories, but it's quite valuable to the Panel in making plans to move forward, so we thank you again.

We will now take a 10-minute recess and reconvene at 4:05.

(Off the record at 3:56 p.m.)

(On the record at 4:07 p.m.)

DR. LEWIS: We will now begin with the Panel deliberations. The floor will be limited during this discussion to the experts here around the table and the FDA staff to begin deliberating on any thoughts you may have about the information you've heard today or the material in the packets that you have received. The portion is open to the public observers in the audience, but you may not participate unless someone on the Panel

specifically requests information from what you said before.

For the Panel members, please take out your questions that were presented to you by the General and Plastic Surgery Devices Advisory Committee. We will address these topics. There are seven topics of which six require immediate Panel deliberation, the last is something that can be done at the end of the day tomorrow. The first subject is related to registries. The Panel will be asked to discuss how best to modify and utilize breast implant registries for data generation characterizing longitudinal outcomes to better inform patient care. And there are two questions beneath that.

First is please discuss how to utilize breast implant registries for data generation characterizing individual [sic] outcomes to better inform BIA-ALCL and BII patient care.

The second is shortcomings cited by some people regarding the PROFILE registry and NBIR include data entry by physicians, limited data access, and data gathered being limited to reoperations. Others consider these shortcomings to be things that promote high quality, consistent data collection.

We'll address both of these questions as a single subject, and I have asked two Panel members to begin with commenting on each question that we will deal with subsequently and to recapitulate and summarize in a short period the information we have to date to frame the questions for this -- for Questions 1 and 2. Dr. Ann Marilyn Leitch and Dr. Karla Ballman are the two Panel members who will be dealing with that.

Following their presentation, we will then open the Panel to an open discussion and attempt to answer the questions. If it would be possible to put both of the questions up on the screens, that would be helpful. The time, total time, we have is 2 hours in deliberation. We need to cover the first two major subject areas. The first is registries; the second is BIA-ALCL. And if we have time, we will begin the third question, which deals with breast implant illness. If not, we will carry that over to the first discussion session tomorrow. So,

I'd like to begin.

Dr. Leitch, if you would lead off.

DR. LEITCH: So, we heard about several registries that exist to help define what's going on with patients who get breast implants and all of them seem to have aspects that are good and can help to elucidate this, but there are also some practicalities that we need to think about and problems that exist that haven't yet been sorted out.

So, one issue is what is the denominator? It's kind of surprising that we can't know exactly how many implants are put in and the relative number of problems that exist compared to that number. Hopefully, the National Breast Cancer Registry -- excuse me, Breast Implant Registry would get to that, but it's just now getting under way.

The other issue is when we're trying to figure out symptoms and their prevalence within the implant population and its comparison, what is a good control population to compare to?

The other consideration was when you have all these registries, would it be more efficient to try to consolidate the registries so that the physicians who are entering or the patients who are entering essentially have one source to go to for entry rather than multiple sites?

And then some other practicalities to be thinking about, we saw one registry having 85 questions that are asked of the patient; you know, is that reasonable and likely to be filled out? Maybe a patient who's having a lot of problems will do that, but a patient who is doing fine may be unwilling to go through a list of 85 symptoms to check them off.

Another practical issue in terms of follow-up is compliance and this is compliance from the patient side and compliance from the physician side. Realistically, you know, if you think of some of these problems appearing, you know, in the past 5 or 10 years, are those patients actually seeing their plastic surgeons at that time, and are the plastic

surgeons, you know, going to be the ones that can reasonably enter data about those patients if they're not seeing the plastic surgeon?

So, I think one of the persons talked about, you know, a letter to all physicians. I think one thing we might think about is for the patients who have breast cancer, they are followed in long term often by the surgeon that took care of them, the medical oncologist or survivorship clinic that exists at the facility where they're treated, and so there is the opportunity for those patients to be followed on a regular basis without extra visits for them for follow-up. And I think engaging other physicians who are involved in the care of these patients to get the data is probably a good idea. The question is, again, how do we get that, make that happen?

And then trying to figure out what are the questions that are most important, symptoms that are most important, that are likely to pick up those ones who are having severe problems rather than so limit the system -- the symptom list and look at specifics like referrals to rheumatology or other physicians to identify certain symptoms. That might be a way of ascertaining whether there's a problem or not, rather than an exhaustive list that may be more difficult to get compliance with filling out.

And I'll turn it over to Dr. Ballman to add any other thoughts that she has.

DR. BALLMAN: Thank you, Dr. Leitch. That was a really good summary.

Just to amplify on a couple of things, I mean, I think, you know, we need to -- the registries need to think carefully. It would be good to capture everyone, but if it's 17,000 patients a day, who's going to do the data management on that, and that's going to be very costly. So being a statistician, you do not need to have a complete census in order to understand what's going on. So some thought about potentially, I think we do need to capture and track all devices, we do need that information, but in terms of the more in-depth information, I think a really good representative sample can do that just as well, if

not better, because you can concentrate on getting high quality complete data rather than trying to cover everything and being left with just a little bit, so I think there might be some thought in that.

How frequently to query might also be given some thought. We've heard a lot about annual, but is annual really necessary? The Women's Health Initiative studies, the National Health studies, so forth, would query every 2 years, and they would get some really good data. So, again, how often, that might be something to think about.

And then we heard, too, and I think it's very important, especially with the international registry, that standardization of whatever's collected is probably something very important to think about so that registries across the world can be sort of combined together, but I think those are some of the things we heard today.

DR. LEWIS: The first sub-question to Number 1 is please list the highest priority questions to be addressed using breast implant registries. Could we focus on that and have the Panel provide their own thoughts about that?

Dr. Li.

DR. LI: One thing that, for me, that's missing out of these registries, including the NBIR, is the device. We spend a lot of -- all the time is spent, rightfully so, on the patient and symptoms and etiology, but devices are not specifically pointed out. In our panel pack they said there were eight devices that were approved for use in the U.S., but it's really more than eight because some of them you could get textured or smooth, so there's really something like 16 in the U.S. And I have a paper here on my computer that analyzed the surface temperature of 13 different implants worldwide. So even to say textured, I think, is a poor description of an implant.

So if there is, for instance, a device tracking ID or a barcode, it seems -- I say this in the nicest way, it seems like the Center for Devices and Radiological Health should require

that the device be named in the database, otherwise we'll never really get to the actual device; we're just going to keep blaming it on texture when texture could mean one of maybe 20 different textures. And I guess right now it just seems like there's one texture that is getting most of the attention, the Biocell, but there are other implants around the world that have virtually the same texture by any physical description but don't seem to have the same clinical performance.

So, it seems to me it's something other than in addition to texture. You know, is the texture such that it's just incredibly bad luck that they picked the exact wrong size or the wrong depth to make the bacteria preferentially do something there that it doesn't do in all the other implants, or is there something else going on? But I think if we don't identify specifically the implant, we're forever going to be trying to guess what the cause of the problems are.

DR. LEWIS: If I heard correctly, the implant manufacturers have barcoded the implant so that that data, if a registry is operating, could record it fairly seamlessly.

DR. LI: That would be ideal.

DR. LEWIS: And that would presumably have all the characteristics of the implant. For the manufacturers, is that a true statement that we can rely on?

(Off microphone responses.)

DR. LEWIS: Okay, I see a lot of nodding heads, so I assume that's true. So, the mechanism for getting that data seems to be in place to transfer that data, even though it's complex, the barcoding should allow that to occur. So that problem would not seem to be so difficult. The bigger problem is the registry itself, how to construct the registry and how to operate it.

DR. LI: I raised this because of being involved in registries for several other devices. This is always the missing piece of information in the registries, is the device itself. So, it

seems trivial, but it always seems to get left out. And, actually, even for those patient groups on social media that we've heard a lot today, the self-reporting, it would help if you're self-reporting if you could find out what device you actually got rather than say a company name and it was textured because there are more than one option. So, the more specific information you can get in the database, the better chance we have of identifying what the problem might be if it's device related.

DR. LEWIS: I think we would all agree and accept that complete information about the device is essential.

What other elements, to refer to 1a again, do people feel need to be included in the registry?

Dr. Leitch. I'm sorry.

Dr. Burke.

DR. BURKE: I think we've heard a lot about possible predisposing existing possible conditions like we should, in this registry, now find. Did people have lots of allergies before? Is there a family history of connective tissue disease? Do they know of immunodeficiency diseases in the family, or have they had any diagnosis of an immune deficiency disease after -- when they've gotten symptoms or not gotten symptoms? Do they take vitamins, do they take Vitamin D? So, I think that I agree that we should not make -- that there should not be a registry of 85 questions, but I think that one small segment could have certain questions about these possible preexisting, predisposing consequences.

DR. LEWIS: Okay.

Yes, Dr. Lippman.

DR. LIPPMAN: Yes. I'm not quite sure how to incorporate this in the registry, but it worries me greatly about this. Notwithstanding the evidence that we've heard, that many of these extremely unhappy symptoms may relate to implants, many of these diseases and

symptoms are extremely common. Rheumatoid arthritis, lupus, Hashimoto's disease, all kinds of connective tissue disorders are extremely common, and when an extremely common thing being done 300,000 times a year collides with something else that's common, attribution, just because it happened to a person, however sorry I am for that, doesn't prove the connection.

So, my worry about these databases is that is there any way we can have something that we develop alongside of it that says compared to what. In other words, if we looked -- and I'm speaking, not proposing, suggesting a thought. For example, if you looked at women who have had all the stress and all the trauma of aromatase inhibitors and mastectomy and whatever who don't get reconstructed, these are some very unhappy and harmed people, no question about it. So, I'm very concerned that you might create a tremendous database, accumulate hundreds of data points about these patients, and then not know quite what to compare it to, and that would be a catastrophe, I think.

DR. LEWIS: Yes, Dr. Rogers.

DR. ROGERS: One of the things that struck me in looking at the data that were presented to us was the reoperation rate for these devices, and to me, that's a very concrete measurable harm to patients, and if it's as high as 1 in 4, that just is astounding, to me. And so one of the things, I think the life cycle of the implants, to be able to better characterize the life cycle of the implant would help patients inform, make informed decisions more -- even more than really rare events, which are tremendously harmful and debilitating, but I can't imagine that having, you know, a reoperation for an implant that you thought you were going to have forever is not also associated with harm. So, I'd like to see some of those hard outcomes about the life cycle, the implant, in most individuals included.

DR. LEWIS: Well, there are some clearly defined complications which occur

anywhere from a few percent to 25%, rupture, contracture, displacement, etc. It seems to me, clearly, we want outcome measures for those things, the well-defined complications.

DR. ROGERS: Yes.

DR. LEWIS: So that would be the second set, and that would be the indication for operations, generally. So, I think we need both the diagnoses of the specific malfunction of the implant and data regarding the reoperation and when and how it's done.

DR. ROGERS: Yes.

DR. LEWIS: Would there be consensus around that?

Dr. McGrath.

DR. McGRATH: I agree with you. I think that the basic registry has to be parsimonious. It can't be massively comprehensive.

DR. LEWIS: Correct.

DR. McGRATH: Nothing will happen. You have to pick out the top dozen or so things. Then how are you going to get the periodic follow-up, and how are you going to get the death? I think the answer is -- was a presentation we heard today about the Aesthetic Neural Network. What they're talking about there, if I understand it correctly, is linking to the patient's electronic medical record, and if that could happen, if all the privacy possibilities and so forth could happen, that the registry then could truly become linked to the patient's electronic record. As those become more robust, then you could go directly to that for your follow-up information rather than having to query people. I think we ought to explore that, whether that would be a valuable and useful thing, to really press on as a way to go forward.

DR. LEWIS: Yes, Dr. Ballman.

DR. BALLMAN: So, I'm part of ASCO, and they have what's called CancerLinQ where they're uploading oncology medical records, and it's a mess, where we're not able to get

anything out of it meaningful. We can't get tumor response, for instance. We can trust death. But, you know, it -- so I think that's something we need to work on. I'm not pooh-poohing that; I think that definitely is something to explore.

On the other hand, I'm also part of, tangentially, the All of Us, which is the big NIH sort of collection of samples from people to try to predict based on genetics and what's in their samples, what's going to happen to them in the future, and there, they're following patients just by email. Every 2 years the patients get a survey and fill that out. And so, I think they're somewhere in between right now that we can shoot for.

DR. LEWIS: Yes.

DR. PORTIS: I think, too -- and I know we'll get to it with the other questions, that the registry alone isn't going to solve for everything, that it's a multifactorial problem, and we're going to talk more about informed consent. I think it's just one piece, that a registry can't do everything. We have to do more of the foundational work, too, of making sure doctors have the information that they need, making sure patients are given -- and I know, again, we're going to talk about it in a later question, but much better, informed consent. So, I think the registry is only one piece of a big picture.

DR. LEWIS: Yes. Yes, Dr. Sandler.

DR. SANDLER: Just to continue on the registry issue, I do, obviously because of the questions I ask, have some concerns about the control group. But somebody presented an Israeli study today where -- and thanks to Dr. Li, I was able to review the paper, and what they did was they identified a very well annotated administrative database in their country, and they were therefore able to identify large numbers of women who had had a breast implant and found a control population of women and then identified the incidence, in their database because these patients had been followed, of collagen vascular diseases.

And while a registry is a great idea, it's just so hard, and it's so time consuming, and

there's always going to be questions about are you getting all the information into each cell that you want populated. But I'm just sort of wondering whether we can do some looking back now, like right away, if there's high-quality databases. I'm just thinking, you know, the Kaiser system or, you know, the VA system wouldn't work, but systems like that that might provide data that could be mined right away.

DR. LEWIS: I think, in view of the difficulty the FDA has had in trying to do any of this in the past, we'd be better to look forward and see, assuming that we have a will to do something different, ask how to do that so that we can gather data prospectively that will be effective. I think, looking back, we'd open a whole range of other things. I'd like to stay focused as much as we can on 1a, which is what is it you want to measure.

Dr. Ashar.

DR. ASHAR: Right. I think, you know, I appreciate the conversation around this, it is a big concept of the registry, but I would turn your attention to 1a and the highest priority questions, because once you identify the questions, then you can think about what the appropriate control might be and what the appropriate strategies might be. But truly, what would be helpful is knowing what the key items are as a first step, recognizing that we'll go back and address other questions as we get more experience with the registry.

DR. LEWIS: Dr. Anderson.

DR. ANDERSON: I agree with the point that Mark Lippman was making about tracking women, and I'm thinking very specifically of BII, and that is that these women are suffering from symptoms that are in this rheumatological arena, that it's in that same family as fibromyalgia and chronic fatigue and these other disorders that are not well characterized, and that part of the problem for our community is that there's no -- it's not a diagnosis, it's a set of symptoms. I think that for a registry, what we want to have, you can't make it every question. What we need is a core set of questions that -- and being advised

by somebody in rheumatology, not thinking just about implants but about this family of disorders so that we could then identify a cohort that we would then go and study in greater detail. So, core questions rheumatology-based to get at that family of symptoms that are so clearly terrible for our patients.

DR. LEWIS: Good, glad you brought that up because that was where I was leading next. It seems to me, in view of what's recorded and what we've heard here today, that some method of recording BII, whatever you call it, whatever name you might give it in the future, is going to be exceedingly difficult because at different times up to a hundred different symptoms have been listed, most of which are difficult to quantify. And so, we clearly need to have measures of that to be recorded in the tracking of these patients, but the question is how do we focus on, perhaps, a limited number of symptoms that are more common in order to identify the occurrence of that? And I would appreciate comments from the Panel if they have ideas on how to approach that issue.

Yes.

DR. ROGERS: I think that part of what has to happen is that there needs to be development of new symptom severity scales and measures to capture these problems, that ad hoc questions are not going to be reflective of the patient experience, and I know we had mentioned BREAST-Q as, you know, a validated measure. Maybe that's part of it; it's not going to necessarily get at maybe some of the other symptoms that people are experiencing. So, I'd like to see patients -- patient-driven with patient input into the development of measures. Many of our PROs have never been developed with the patient input, and those, then, you can get down to more parsimonious amounts of questions. But to do it right, we need validated and reliable measures.

DR. LEWIS: So, some method of arriving at a more standardized set of measures of the -- perhaps the commonest symptoms that are seen with BII, it seems to me would be an

essential start and a method, hopefully, of grading those in some way.

Yes.

DR. GALLAGHER: So, I'm wondering -- I mean, I know this all will eventually go into the registry, but I'm thinking about the whole idea that BII is probably more common than the ALCL, and so therefore I think that we should really be talking in some parts about how to identify BII as a syndrome. And so I think the comments about looking at it through a rheumatological thing are important, but I also think that there was mention of a CD30 marker and some other genetic markers, so I think that we would have to also consider is there a genetic component that could be identified or several components that might eventually be identified that could become a part of that process.

DR. LEWIS: Well, that was actually what Dr. Lippman was speaking about in terms of the relevant history of any immune or rheumatologic illness in the patient or the family, correct me if I'm wrong. So, we have two elements; one is a history element regarding the patient coming into the implant, and the other is the occurrence of BII subsequent to the implant. Symptoms may be related, but there are two different sets of data, and we'd need -- one would be a need to -- be recorded at entry and the other in tracking after some period of time. But I think both of those would be things that ideally would be required. Are there other comments regarding that?

DR. BALLMAN: Just to refine, like, an important question a little bit more. I think the question of BII is -- it should be sort of top priority because that's what we've been hearing a lot about today, but not just BII in general, but also is it associated, as brought up, what specific types of devices or specific characteristics of devices, which Dr. Li had sort of mentioned.

DR. LEWIS: The other obvious choice is ALCL, we haven't mentioned that as a specific entity, but clearly, that also needs to be one of the things recorded and all of the

parameters related to that in terms of how it's diagnosed and identified. The criteria, obviously, for diagnosing that are far more concrete than BII, but it clearly is another outcome that needs to be measured.

So, we now have, in essence, tracking of the patient regarding the occurrence of the standard, more common complications related to the device itself, the occurrence of BII to be characterized and the occurrence of ALCL, specific data elements. Are there other elements relative to the performance of implants and the occurrence of subsequent disease that we need to deal with?

Dr. Lippman.

DR. LIPPMAN: I had never heard it before, but I was deeply touched by the stories two women told about their offspring and nursing, and it's impossible to know how to make an attribution on that basis no matter how sorry that story is, but I believe it's an element we ought to try to record because it's so devastating were it to be true.

DR. LEWIS: Do you want to comment?

(Pause.)

DR. LEWIS: Dr. Li?

DR. LI: Just for clarification, are we talking about kind of starting with a whole new registry or just kind of augmenting the registry that we've got now?

DR. LEWIS: We really --

DR. LI: Or the MDR or something or NBIR? Excuse me?

DR. LEWIS: We haven't made that choice.

DR. LI: Okay. And maybe this is obvious, that it should -- should it be required, as I -- actually, I was looking through the MDR, it's not always listed in the MDR why the revision or reconstruction or second surgery was done, and we've heard, by some of the speakers, associations of ALCL with contracture or with rupture, but those things, if those are

somehow associated, they should also be captured in the registry. So, I was really kind of looking at --

DR. LEWIS: Are you speaking about the indications for surgery in the first place?

DR. LI: The indications for surgery. So, if there's a connection between, say, contracture or rupture and ALCL, that it would actually somehow expose itself.

DR. LEWIS: Well, maybe we could capture it more generally by citing patient demographics coming into the implant, which would include not only straightforward things like age and so forth but would also include the disease process which led to the implant.

DR. LI: That would be fine just so long as there's a way that it's clear that information should be there as opposed to kind of a choice that it should be there.

DR. LEWIS: So, we have input data, patient demographics, including disease and indication for surgery. We have the implant characteristics. We have personal or family history of rheumatologic disease and/or autoimmune disease. And as outcome measures, we have the macroscopic complications that are well recognized with implants, physical complications, the BII occurrence with specific indicators and characteristics to be defined, and we have ALCL. So, we have three inputs and three outputs, as it were, to be tracked. Have we missed anything? Is there anything else in the idealized world that we think should be measured?

(No response.)

DR. LEWIS: Dr. Ashar, have we answered 1a?

DR. ASHAR: Yes, you have. Thank you.

DR. LEWIS: Let's turn to 1b. Please consider whether modifications to the existing registries are needed to address these questions. If so, what modifications do you recommend?

Dr. Leitch.

DR. LEITCH: Well, I think consolidation is an obvious place to start, you know, to -- rather than having four different registries, having one registry that then you can dive deeper into, you know, if you have a case of ALCL that you can -- then you go down that path deeper. But rather than having them all separate where people have to kind of decide which one am I going to participate in, which one do I go to, I think it would simplify the process if it were -- you know, if it were consolidated. So, I think that's a -- that's something that should be strongly considered to do.

DR. LEWIS: Yes, Dr. Burke.

DR. BURKE: Well, I absolutely agree with consolidation, but the problem is you have to be sure you don't get redundancy, that the same people are reporting within two registries. I mean, that's a potential difficulty, but absolutely --

DR. LEITCH: No, just have one.

DR. BURKE: -- we must consolidate. Yes, just have one registry.

DR. LEITCH: Just one registry, that way you don't --

DR. BURKE: Yes.

DR. LEITCH: -- have the implication because --

DR. BURKE: Exactly, one registry.

DR. LEITCH: -- you do have -- I'm sure right now patients are reported in multiple different registries.

DR. BURKE: In different places and in different ways.

DR. LEITCH: Until you have -- you do have duplication of data, and you got to figure out how many duplicates do you have and sorting that, which -- you know, that's already been talked about and trying to figure out the number of cases of lymphoma is duplicate reporting. So, one entry point --

DR. BURKE: For everyone.

DR. LEITCH: -- would reduce that, and that doesn't necessarily mean that you couldn't have two physicians entering the same patient. That could still happen, but if it could be tied to the barcode of the implant, that might solve that problem.

DR. McGRATH: Yeah, I think that this question -- I think we can just sort of give some broad lines here, but really, in the end, I think that the people who are working on the National -- U.S. National Breast Implant Registry need to sit down with the ones doing the ICOBRA, which is the international registry, and everybody really needs to come to a table and agree on these things because otherwise we're not going to get the worldwide data that we need. And we should because it's the same devices everywhere.

DR. LEWIS: Well, I only have a superficial knowledge of it, but it sounds as if the structure that's currently in place and being organized for the NBIR offers the promise of a nucleus that could be augmented and, if suitable governance and funding and support were available, perhaps expanded to meet the needs. Do people see -- have a different view of how to go forward with that? Do you see that some other group should be urged to create the registry? Should support for NBIR be recommended?

Yes, Dr. Rogers.

DR. ROGERS: One of the things I wondered about was what percentage of these procedures are performed by plastic surgeons who might be a member of the society and then familiar with the registry versus not.

DR. LEWIS: Somewhere in the data we received it said about 75% are done by plastic surgeons. I don't know if that's totally reliable, but that's the ballpark figure.

DR. ROGERS: I think I would just like to echo once again, you know, entry and entering data into registries is very laborious, and in urogynecology we've had a number of registries that have struggled because it puts a lot of burden on the physician to enter data and you're busy and the feedback. So, if there's a way to do sampling, like NSQIP or

something like that, which is a little bit less onerous on the individual but gives you great benchmark data, I think that would be really helpful because it's not only a burden on the physician but on the patient. It uses up time and resources. We'd like to have everybody in it, but do we really need it, and is it worth the burden both in time and cost?

DR. LEWIS: Is there -- yes, Dr. Brummert.

MS. BRUMMERT: The existing registries, is the information made public, or is it private? Because it seems transparency is important to the victims that came here today, and I'm wondering if they have access to any of the registries that we've been talking about.

(Off microphone response.)

MS. BRUMMERT: Okay, if the answer is no, is there a way to incorporate that into a registry?

DR. LEWIS: Dr. Ashar, can you answer that?

DR. ASHAR: No, I was just going to say that Andrea Pusic may be able to comment on that, but I know periodically the organizations do publications similar to the PROFILE publication recently in March.

MS. BRUMMERT: I mean, is that a summary, or is it more in-depth data that victims deserve to have?

DR. ASHAR: It's a literature article summarizing the reports that they had received to date.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: So, I don't know how useful it would be to have access to like, you know, 400,000 individual data points. But I think what would be helpful is if like, you know, there's a periodic report, you know, that that's reported out like, you know, quarterly or something of here's the percentage of adverse events, sort of seeing here's the percentage of patients that had to go -- undergo reoperation and things like that, and I think that would

be something that's doable and could be posted on a public website. But I don't have any say in that.

DR. LEWIS: Should the FDA take a role as a convener among the current people who are involved in registries in pulling this together, and if not, who should do that? The plastic surgical organization, I gather, is central in supporting that. How do you involve all of the stakeholders who have a role and stake in the registry, including patients, obviously, in arriving at a structure to manage this?

DR. ASHAR: I was wondering if it might helpful for Dr. Pusic to come to the microphone and just explain what is reported and what's publicly available regarding the registries and what's not. If that's okay?

DR. LEWIS: That would be fine.

Dr. Pusic.

DR. PUSIC: Yeah, I'm just happy to answer any specific questions. Just for clarity, in terms of the sense that there's multiple registries going on, just to clarify, it really is -- the National Breast Implant Registry is our society's registry for all breast implant patients and then PROFILE is a rare disease clinical registry. ICOBRA, which is the International Collaboration of Breast Implant Registries, is a collaboration of multiple countries working together, essentially linking our NBIR with the Dutch registry, with the Australian registry, so there's not a multitude of registries. It may have been confusing in my slide when I said our Plastic Surgery Registries Network; those are completely unrelated to breast implants. The NBIR is the registry for implants.

In terms of the data that's collected within our National Breast Implant Registry, we've worked with stakeholders in terms of patients, the FDA, the industry manufacturers, asking exactly this kind of conversation about what's the most important thing that we should be measuring and asking the fewest questions but the highest quality data. So they

are the clinically relevant pieces of information that we know we need on all patients and reasons for reoperation is probably the key one plus basically everything that you folks have been pointing out, which is the patient demographics, some very simple questions about history of autoimmune and rheumatologic diseases, but very short, very short, but with the view that when we can also do deeper sub-studies and we can ask more questions in specific larger cohorts of patients but nested within the registry.

So, it really is -- the case report form is very short, we've been very mindful of the burden on physicians and the OR staff and not wanting to make it laborious. On the other hand, we, as plastic surgeons, feel that this information is extremely important to patient safety, and we are willing to enter this data, so we've got it as short as we can, but it has to be key data. So, as an example, the reasons for reoperation, a surgeon has to talk about that because a surgeon knows that it has to be valid, so structured data and focusing on validity but keeping it short.

DR. LEWIS: Dr. Pusic, what -- or can you tell us how the FDA and/or other organizations could best be supportive of moving forward with what you're describing?

DR. PUSIC: Thank you. I think, as I said earlier, I think that we are at a point where when a device is placed into a healthy woman in 2018, 2019 now, that we need to be able to support, as a community, the long-term safety surveillance for many, many years, and so that is why I think that our efforts around the National Breast Implant Registry should be mandatory because I think it's just good care.

DR. LEWIS: Mandatory for all implants?

DR. PUSIC: For breast implants being placed in a woman, um-hum.

DR. LEWIS: Yes, for breast implants.

DR. PUSIC: Correct.

DR. LEWIS: Okay.

Yes, Dr. Leitch.

DR. LEITCH: But do you think that these patients will be followed by plastic surgeons on an annual basis or an every other year basis?

DR. PUSIC: The expectation is not that they would be followed annually by their plastic surgeons. So, our registry is set up such that when that patient has an operation or a reoperation, that triggers her again as an event in the registry, so it's not based on an annual follow-up with a physician. What we do envision is -- and it may not be annually, it might be on an every 2-year or 5-year basis, that we interact directly with the patient and ask how she's doing and that's the symptom assessment.

DR. LEWIS: You're saying the registry personnel would interact directly with the patient?

DR. PUSIC: By sending out, as the Australian registry has done, a very brief number of symptoms. I would say one of the things, and I think the FDA has been really innovative in this regard and it speaks to a bigger philosophy and a strategy around device surveillance overall, but linking, and I mentioned it briefly, was the coordinated registries network and being able to coordinate potentially with other registries, other women's health registries, so if a woman isn't being seen by a plastic surgeon but perhaps she's being seen by a gynecologist and so we are starting to be a community of registries.

DR. LEITCH: But what if the reoperation wasn't done by the same surgeon?

DR. PUSIC: So that's why we need the mandatory nature. We need to have all of our surgeons on board so that if I put in a woman's breast implant and she goes to see someone in -- and I'm in Boston and she ends up having it removed and replaced in Cincinnati, I need -- the registry needs to be able to see that and that's -- so that's exactly why we need to have a blanket across the country, which is what's happened in the Netherlands.

DR. BALLMAN: So, you know, the National Cancer Database tries to capture

basically, you know, they capture about 70% of all newly diagnosed cancer, right? But they have some carrots there, I mean, because it's still a lot of data to enter, especially at baseline, and you know, I think it's a lofty goal and I think there are really impassioned people that will do this, but to make it mandatory for everyone without any sort of incentive, do you really think that's realistic?

DR. PUSIC: Well, I think if you picture it -- so device tracking information, if you picture our case report form, so this is our case report form, device tracking is the first half of it, so that is already mandatory and then we ask a very few key questions in addition. And so, we know the device tracking information has to be completed, so what we're just doing is tacking that on.

DR. BALLMAN: But how would that get at sort of, you know, the questions of, you know, the breast immune illness, I mean, or implant illness, you know, for the genetic predisposition and all sorts of questions like that, I mean, how would this database be able to answer those questions?

DR. PUSIC: So those would be nested sub-studies within the greater architecture of the National Breast Implant Registry, and those would be questions to be answered directly by women in that sub-study, not by their physicians.

DR. LEITCH: I thought you said, or somebody said earlier that the validation of disease processes, you know, a specific diagnosis of a rheumatologic disorder would have to be -- would be verified by physicians at the visits.

DR. PUSIC: So, if we were doing a sub-study looking at -- I think there's -- the National Breast Implant Registry, we're looking at operation and reoperation. If we do a sub-study within there, then we could -- in that sub-study, so not the overall patient population of all patients in the National Breast Implant Registry, but we could have a limited cohort that would have their diagnoses verified by a physician because I agree with

you, I think that's very important.

DR. LEWIS: Do you envision any information coming directly from the patient into the registry?

DR. PUSIC: I do. I think that we should -- this is where patients are telling us about their symptoms and about their perceptions of outcomes, but that's the information that only patients can know and tell us about. I think that in terms of data quality and validity of the data, that physicians should be the persons telling -- person telling us the reason for reoperation, and I think the device information should be coming from barcode scanning, so different pieces of the puzzle each telling us -- each the source of the most accurate information.

DR. LEWIS: And as I gather from your statements, you consider the tracking to be event driven rather than time driven.

DR. PUSIC: Correct. So, at the time of operation, the barcode scanning app, we scan that event, the event is operation or reoperation, and all the information, thanks to the FDA's GUDID database, all the information about that implant is -- it can be extracted from that. So, it's not textured versus not textured. We are able to extract from that all the information about the specific make, model, and the type of texturing and all the information that is maintained in the FDA's GUDID database.

DR. LEWIS: How do you anticipate that all of the surgeons involved would, in fact, be willing to submit this data?

DR. PUSIC: I think, again, it's the key pieces that's already part of device tracking information, and we're only asking for a little bit more, and we're not asking for something -- for someone to see a patient on a regular basis, it's all keyed around the clinically meaningful event of being in the operating room. So, in my own operating rooms, instead of now us doing a piece of paper, it's going online, doing the device tracking and answering

another little half-page of questions. So, we're really not asking a lot of our surgeons. And we've worked really closely with our surgeons through feedback, focus groups, making it ease of use, and our surgeons have been very accepting of that.

DR. LEWIS: Given the large number of implants, we spoke before that the current rates are about 1,700 a day, do you see any strategies for doing a sampling methodology to reduce the data requirements?

DR. PUSIC: I do, and I think it's a great suggestion. What I envision, though, is we still need some piece of it that mirrors the device tracking, so all patients entered in. But where we have a specific question, I absolutely agree, we don't actually need -- we certainly -- to answer a question about rates of reoperation, we don't need every -- from a sample size factor, we don't need that on all those patients, we'll have that answer very quickly, and we can resample it at different time points and continue to watch that. But absolutely, I think from a sampling perspective, the idea is minimal burden but broad and then deep in different areas.

DR. LEWIS: Thank you.

DR. PUSIC: Thank you.

DR. LEWIS: We appreciate your -- all of your participation.

Among the remaining questions, Dr. Ashar, it seems to me we have largely answered all of the questions in 1 and 2. Are there other specific things that you would like us to address?

DR. ASHAR: I think we're all set, thank you.

DR. LEWIS: Good. Then we will move on to the second subject, which is the Panel will be asked to make recommendations regarding next steps for the characterization of BIA-ALCL incidents and its risk factors. And the people who have been asked to open the discussion on this, frame the question, are Dr. McGrath and Dr. Lippman.

DR. McGRATH: So, to summarize in 3 minutes what we have heard today about the breast implant ALCL, we have heard that it's relatively uncommon, if not rare; that there are probably somewhere in the range of 675 cases worldwide; that whatever is the etiology or the associated factors, they're clearly multifactorial. There are some that are patient factors which may be genetic or immunologic, as has come up today. That right now we don't have research -- research hasn't taken us to a point where we have a diagnostic test that we could do on a patient to determine if they would be at high risk for the disease either with regard to genetics or immune.

The second thing we've heard is the second factor is physician or surgeon-related factors. We heard several times about the 14 steps that can be taken when putting in an implant to help to minimize surface contamination to hopefully change the biofilm and the bacteria on the implant and that this may be validated at some point, it seems to have some effectiveness.

The third thing we heard about is the implant factors, and that has pretty much focused on surface characteristics. We heard that about 10% of the implants in the United States that are used are textured, and yet probably 95, maybe 100% of the ALCL cases in the United States are on the textured implants. So, it's pointing us in the direction that we need to look pretty closely at that surface -- the surface area and surface treatment.

If we go to the studies that were done in Australia by Deva, there was a way to classify or stratify the development of the ALCL related to the degree of texture on the surface of the implant and that the ones that are the salt cure or the heavily -- the ones that are like honeycomb or a sponge have 16 times a greater chance of having the ALCL than the ones that are the imprinted type of model. I think there's probably places that we can, in our discussion, focus more there. We've heard that there is ongoing -- in fact, there's robust research coming down right now to keep this up, looking at all of these questions,

particularly the patient factors, the inflammatory disease. We're not going to talk -- we heard a lot about data dissemination, but we'll save that for tomorrow.

And I think I just wanted to add one thing that we didn't hear because I think this is really important for someone to say it, and someone who's a plastic surgeon to say it, that there is a benefit to the texturing that is not just cosmetic or aesthetic. Nowadays there's a much greater chance that women will be having bilateral mastectomy, and they will be having skin-sparing mastectomy or even total skin-sparing mastectomy, and this was not true 10 years ago, this is new, and with this the very best reconstruction, the most straightforward way really is going to an implant, and to put a smooth surface implant in there is very problematic because it doesn't stay in the right place, doesn't sit right. So, the texturing has given us an opportunity to fix the implant, so the stability of the implant is better with the texturing.

DR. LEITCH: How do you think that --

DR. McGRATH: Now, I got --

DR. LEITCH: -- plastic surgeons have gone to that, though?

DR. McGRATH: Well, here's what's happening. This is tomorrow's discussion. Those who have chosen to not use a textured implant, which is a big chunk because people are moving away from it, going back to the smooth, they're wrapping them in mesh to get the same effect. So, in effect, what we're going to be -- the ADMs are all being put there to make up for taking away the texturing, so it all links together in a way that I just think is important to share with you because this -- if you're not doing this clinically, this may not be immediately obvious.

DR. LEWIS: Dr. Lippman.

DR. LIPPMAN: Yes, Dr. McGrath has stated much of this in a way that I'll be slightly repetitive about, and then I will add a little bit to it. So, I think we can say that we -- that

ALCL related to breast implant surgery exists, but I'm still somewhat ill at ease at what the true incidence actually is. We've heard that the median time is 10 years, and since these are going in at an ever-increasing rate, I think it remains to be seen exactly how much the true incidence is in this disease.

Obviously, we've heard a lot of compelling evidence that it's related in part to smooth versus textured, but we've heard significant evidence that there's a great deal of difference between them, and that gets to the notions of informed consent and risk. I mean, is telling someone they have one chance in 3,300 of getting a lymphoma a reason to ban it or to change your informed consent? Is telling someone that they have -- it's a rhetorical question for the moment, please. Is telling them that they have a risk of 1 in 86,000, which is less than the risk of general anesthesia for the procedure, is that something that you would just do by informed consent? And we've heard risks for different prostheses that are in that range.

I think it's essential to have more information about the etiology because if this is a biofilm inflammatory bacterial issue, it may or may not be resolvable without having to deal with the implant but by some surgical technique pre- or postop, that would be worth exploring, and I think that's critical.

I think a question that has not come up, but I wish it would, so I'm raising it, is whether or not the syndromic breast illness in any way relates to the lymphoma. There is a ton of disease for breast cancer about which I'm highly familiar, that stress, inflammation, depression, and all of these other diseases alter greatly the occurrence and recurrence of breast cancer, they're all associated with a series of immunosuppressant inflammatory markers, and I think it's worth asking, in some of these registries, whether or not there's an overlap between those patients most distressed by, let me call them subjective complaints for the moment, and their development of lymphoma, and I think that that is a question

that would really be worth addressing greatly because I think it may tie the entire discussion together. So those are things that I think are on our agenda to discuss.

DR. LEWIS: It seems to me, in the data that was presented by Mentor, and I don't know the total numbers, there was a striking difference in the incidence of ALCL based on the type of texturing. If we assume that all of those methods of texturing have the same benefit to the surgeon in terms of fixation, then what would be needed to basically say we need to get further evidence, and is that the case for the different -- for the roles of the different texturing in ALCL? In other words, if the texturing, the type of texturing as employed by Mentor, in fact, lowers by several fold the incidence of ALCL, that would seem to be an obvious step, first step, to take.

So, to me the question is, is the current evidence adequate, and if not, what is further needed to fully define that relationship and the role of texturing? And to me, going to biological studies to employ mechanisms is a very indirect way to get to it. If you already have data that looks convincing, that the method of texturing, in fact, has a dominant effect, and if you have an obvious way to move to that, why do you need further studies as to why the more complex texturing needs biologic study?

Dr. Li.

DR. LI: I think in general, I --

(Off microphone comment.)

DR. LI: Sorry. I got censored here by the -- sorry. I think my concern is that I'm willing, from the data, to certainly agree that there's one what we've been calling a highly textured implant seems to have a higher incidence of ALCL. I'm very uncomfortable, though, attributing all the causation to just saying that it's highly textured. You know, certainly being highly textured is a very visible difference from the others, but it's not -- I'm not convinced what the mechanism is because in all the texturing except for the ones that

have almost no texture at all, bacteria grows on all of them, there's very little difference in laboratory in vitro studies of growth of bacteria in these. The length of time before the ALCL shows up is over 7 years, so bacteria somehow is either placed on it at the time of surgery and then just sits there and only does one texture, in 8 years turns into ALCL but not in some other texture even though we saw data that says the bacteria in all these implants is the same, so it just doesn't seem to me that it's just texture.

Other things that have been raised up or one you raised earlier about the -- are all the silicones the same? The answer is, from a strict chemical sense, they are not exactly the same. They start with slightly different monomers, they use different catalyst systems, so although you can certainly characterize them in general as silicones, it's relatively easy using strict chemical techniques to demonstrate they are not identical. Now, we always hope that really isn't a biological difference, but given what's going on here, I'm not really willing to remove anything out of it.

And just as a last possibility is -- again, it was mentioned earlier that particulates could cause some transformation that leads to ALCL. So, certainly, if you have a more porous or a more networked surface and that moves at all, you could generate particulate in different sizes.

So, although texturing kind of is the visible difference, it's not clear to me that that's actually the causation. So, in fact, like I said earlier, there's 13 different textures of implants around the world, many of which, by any measure of texture, is the same but they don't have the same clinical performance. So that's a long-winded answer, a way of saying we can call it highly textured, but I would not call that necessarily the causation of the problem. So, the reason why you would look at it more is I wouldn't want to, at this point, just say don't make anything with this texture because there are actually examples of things with similar textures that seem to be okay. So, I would just warn on over-simplifying at this

stage of just making a texture.

DR. LEWIS: I certainly don't think it's necessary to conclude that the texturing is the only factor, but if data in which the only variable is the texturing shows such a striking difference, why do you need more data to say that's important?

DR. LI: Only if there is another implant with similar texture that doesn't behave the same way.

DR. LEWIS: Well, yeah. And that gets back to the basic question I asked first, which is how much more data and what kind of data is needed for the FDA to have confidence in this observation?

DR. LI: Well, I think there's -- in my head there's two questions. One is with this particular implant, the specific implant that's out there that we've got this data on, what should you do about it, you know, should you take it off? Should you, you know, take it off like you're up, or should you leave it on; that's one question. The second question is what do you do about the other implants that have similar or different surface textures? To me, that's two different questions.

So, you know, in answer to your first one you could be like Europe and say, listen, there's enough worry here, let's just take it off, take this one off the market, and they didn't take the others that had similar textures off the market; they just took that one, so I think there's a difference in the two questions.

DR. LEWIS: Dr. Gallagher.

DR. GALLAGHER: And I also wonder, since listening to the testimony of the women in particular, I'm thinking some of them talked about smooth, some of them talked about texture, but also some people talked about textured saline, things like that, so I'm also wondering what are the other ingredients? So, if I think about, you know, somebody wants to do something to my car, they're going to put oil in the car and do I want synthetic oil, do

I want real oil, what do I want in it? I want to know the difference. What else is in it to make a difference? So, I just wonder --

(Applause.)

DR. GALLAGHER: -- if there's something about the characteristics of the implants themselves that goes beyond the texture, that goes beyond the idea of is it a silicone and what kind, but also what is the shell made of that might be causing part of the problem as well.

(Applause.)

DR. LEWIS: Dr. Burke.

DR. BURKE: And I haven't read any studies about anyone analyzing the seroma fluid. In other words, are there any particles of silicone, are there synthetic components, is there acetone, is there formaldehyde, what -- can anything ever be detected in miniscule amounts in the fluid extracted from patients that get the ALCL?

DR. LEWIS: How does the Panel feel the FDA should proceed in regard to this? We had several people who urged that we would advise them to remove textured implants from the market. Does anyone feel we should move ahead with any of that?

MS. BRUMMERT: I actually agree with that. I think there's so many risks, and a lot of these women who get the implants, they had cancer already; then they get the textured implants and they're getting cancer again. I think that's so much of a risk that I think they need to be taken off the market.

(Applause.)

DR. McGRATH: But even that means we have to use something else to stabilize the implant, or there's just going to be a tsunami of additional reoperations and re-surgeries, and those, if you do statistics, may be far more dangerous for people if they have to go back for repeated surgeries because the implant doesn't stay where it is and it doesn't have a

form to it. So that's what we're weighing here. If we felt confident that wrapping the implants with ADM with the mesh was safe and is effective as the texturing, then I would absolutely agree with you, but I don't know that, and there's a real downside to this, too, of completely losing texturing will be very problematic.

DR. LEWIS: Yes.

UNIDENTIFIED SPEAKER: Banned in 33 countries.

DR. LEWIS: Dr. Jaffe.

DR. JAFFE: Yeah. So, I mean, I think we have to look realistically at the incidence of breast implant-associated ALCL. It's exceedingly rare, and in the vast majority of patients, particularly if diagnosed early, it's no, you know, significant risk to mortality or even recurrence. If you diagnose it early, I mean, while it does require surgery and it does require removal of the capsule, that patient should be cured and should not need radiation or chemotherapy. So, I mean, I think there could be better focus on early detection. We know that whenever we see it, there's always an inflammatory milieu, there's a fibrinous exudate, there's seroma fluid. I think, you know, whether it's looking at inflammatory markers serologically that might give us a clue, elevated cytokines, there have been some studies showing that the neoplastic cells elaborate cytokines and that those can be measured in the fluid, so whether, you know, sensitive methods might allow early detection serologically. I think there are a lot of ways to explore short of just banning the implants, which might create new problems because the mesh might create the exact same inflammatory milieu and you're back where you started.

DR. LEWIS: Dr. Lippman.

DR. LIPPMAN: Yes, I think Dr. Jaffe's point couldn't be better stated, and I'd like to amplify a little bit because I think when you say risk, you have to say sort of compared to what. If the best estimate for risk for the best textured transplant, there's 1 in 86,000

incidents and the mortality is perhaps a tenth that, that's close to one in a million people.

Just for comparison purposes, one of the greatest drugs ever invented for breast cancer prevention is tamoxifen. One in 150 women will get a benign form of endometrial cancer and require hysterectomy, which is not exactly a walk in the park, and we think this drug is a fantastic advance, but lethality for daily aspirin far exceeds 1 in 86,000.

So, I think before we just say we're going to have a reflexive "let's take it all off the market," you have to look at what the advantages are. I think a critical issue is certainly informed consent. A woman has every right to say I don't want that, I don't even want the 1 in 86,000, but that's not banning the device. I think that's an extraordinary overreaction.

DR. BALLMAN: Yeah, I mean, I would like to second that. I mean, I worry about the data that are on hand. I mean, I can't believe how bad the postmarketing studies have been and that the companies could get away with not doing a much better job and not having their thing pulled, but I don't know what the FDA does. But on the other hand, you know, I mean, do we want to get into a sweetener situation where we pull one sweetener and the replacement is even worse? And so I think until we really fully understand everything, the best thing we can do is full informed consent so that the women know that this could be a possibility and they really know it's a possibility, but I think a kneejerk reaction of just pulling something without knowing what its replacement is going to be and if it's going to be worse might get us into more trouble.

DR. LEWIS: Dr. Gallagher.

DR. GALLAGHER: I also think -- so I'm not an M.D., I'm an ethicist, so when I talk with patients and their families and physicians and nurses, etc., we talk about risk, benefit, and burden. And I think that's where the informed consent process becomes so important because if it isn't done in a way that helps the patient and whoever's important in their life understand the effects that this might have, what burden it might carry no matter what

kind of surgery you're talking about, then we're missing something.

So, if one of the -- one of the things that I heard, and I did checkmarks, was from several of the women, was that they were asking for a checklist for patients. So, I think the informed consent process becomes important. I don't know that a checklist is helpful. I'm an ethicist, we don't do that kind of stuff, but I think that, you know, some way to say these 10 points have to be covered in the informed consent process or something so that they can look at the risk, the benefit, which doctors are very comfortable talking about, but also the burden that they and their family members might be looking at in the future.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: Is it really true there's no way to track down the cases that already exist to note what specific implant they got?

(Off microphone response.)

DR. LEWIS: I'm sorry. Could we have Dr. Ashar answer that?

DR. ASHAR: Right. So, there's two places where BIA-ALCL is being reported. One is the MDR database where adverse events are reported to FDA and that was the presentation by Karen Nast. That information, they may or may not know the type of implant at the time of BIA-ALCL diagnosis. I think she identified about 30% of the time the implant at the time of diagnosis is unknown. For the others, there may be a cohort where we do know what implant type they had, but it certainly isn't all of them. In the PROFILE registry, and Dr. Clemens and Dr. Pusic may have additional remarks on this, I think they were able to -- they have actually a very detailed registry where they capture all of the information about these BIA-ALCL patients, and this information is inputted by the plastic surgeon who is diagnosing or is treating this patient.

In 50% of those cases, the full history or the full information was not obtained. So, the recent article that was published in March reports on about 48% of those cases, and the

majority of those cases involve textured implants. There was a single digit number, I think maybe, I don't know, 5, 6, maybe 8 patients that had smooth implants, about 64 had textured implants, and then there was maybe about 15 patients where the implant was unknown. But, again, that information in that article didn't report it down to the make and manufacturer type. But we're hoping, with the unique device identifier tracking, that we'll have that more granular information.

And I do want to comment that while I appreciate all of the thoughtful discussion, especially this is such a concerning problem to us, that I understand, you know, where the discussion is going, but understand that we're really trying to do our best to characterize risk. And so what pieces of information can we obtain, request, demand to help characterize risk so that we can minimize harm to patients who might be contemplating breast implants potentially in a place where we can say, you know, you may be susceptible to developing this problem and, you know, maybe we should dissuade you from this decision. Ultimately, many different types of solutions are going to be proposed to fix the mesh or fix the breast implant to the surrounding tissue, and so if we can characterize risk from the outset, I think that would be very helpful to FDA.

DR. LEWIS: Dr. Li.

DR. LI: I just had a quick question for FDA. When you have an orthopedic implant, when you buy a hip or a knee replacement, inside the box with the new replacement there is a set of stickers that have the catalog number and ID number for every individual implant, and when you get a hip replacement, the surgeon takes one of those stickers and places it on the patient chart. So, if you have the patient chart for a hip implant, you can always track back to the actual implant. Is the same thing true for breast implants?

UNIDENTIFIED SPEAKER: No.

DR. CHEVRAY: Yes.

DR. ASHAR: I think we have plastic --

DR. CHEVRAY: Yes, it is.

UNIDENTIFIED SPEAKER: Yes, it is.

DR. CHEVRAY: The breast implants come in a box. There are multiple stickers inside that have the model number and the serial number. One of those stickers is placed in the chart, one of those stickers is placed on a thing that looks like a credit card that we give to the patient, that we're supposed to give to the patient, and most plastic surgeons like myself dictate that model number and serial number into the operative report.

DR. LI: So potentially there is a way to ask -- get some of this data?

DR. LEWIS: Dr. Ashar, do you want to comment on that?

DR. ASHAR: I think there would be. Through the PROFILE registry, the data is being inputted by plastic surgeons who conceivably should have this information available to them to be able to input it in. But, you know, it is a process to input all this data, and so in 50% of the time, the full information has not been reported to do a full analysis on that.

DR. LEWIS: Dr. Portis, did you have a comment?

DR. PORTIS: Well, just to go back to what Dr. Ashar was saying, that if we're talking about risk, it sounds like, yes, maybe that sticker is in the box, but many patients have said they don't have that information, they haven't been fully informed of the risk, and they don't have any idea what implant they're walking around with.

DR. BALLMAN: Well, just to respond to what the FDA said, steps should be taken, you know, what steps should be taken to characterize the risk and implant characteristics. I think we've been talking about that all a lot. I mean, I think we need to know the type of implant that was used, I think we need to know some patient characteristics that might put them at risk, such as family history of, perhaps, immune diseases, you know, so forth and so on. I'm not sure what more they're looking for with 3a.

DR. LEWIS: What more would you like to know beyond what we saw in the data presented regarding the incidence of ALCL with different implant surfaces?

DR. BALLMAN: I don't have any other specific suggestions. I think what we've been talking about would be a help right there. I mean, it sounds like we don't know what textures are being used, we don't know what particular -- we don't know at operation why they had the operation and what they had previously. Were they -- you know, maybe they have a smooth now and they got diagnosed, but maybe their previous one was textured. We don't even know that, and if we captured that and we talked about that before, I think that would help.

DR. LEWIS: Dr. Rogers.

DR. ROGERS: It seems, at the very least, that some kind of mandatory informing the patient about information about their implant with some kind of documentation that that information was passed on.

DR. LEWIS: That's really the subject of tomorrow, I think, in 4 and 7.

DR. ROGERS: Okay. And, you know, I think -- I'd just like to say that, you know, you run away from one thing and you run into the waiting arms of something else, right? So, you know, we have no idea whether mesh is going to have the same problems. Mesh can be very textured and creates capsules and can be a big problem. And so, you know -- and if, again, getting back-- do we have enough data to make a decision about textured implants, maybe, but if somebody's going to make an informed decision, they need more information into the decision than just the adverse outcome of cancer because having a bunch of operations, etc., are going to weigh in to that decision, as well as the many women who won't have the cosmetic result that they're hoping for.

DR. LEWIS: Yes, Dr. --

MS. PAWELSKI: It seems to me that with the hundreds of cases reported, if there's a

third of them or 30% that we don't know, has the industry and FDA worked together to try and track down the 30% of the ones that you don't know?

DR. ASHAR: To the extent that we have --

DR. LEWIS: Dr. Burke.

DR. ASHAR: -- we've provided the information that we have.

DR. LEWIS: I'm sorry, Dr. Ashar.

DR. ASHAR: I think, you know, we've done what we can do through the MDR reports. Our team, you know, this past year found 660 reports. They, by hand, went through with two epidemiologists confirming the information. A lot of the times the MDR reports get supplementary information so you understand kind of what happened to the patient, so they cobbled all that together and came up with, I think, the 440 number, but that's the best information that we have.

DR. LEWIS: Dr. Burke, did you have a question?

DR. BURKE: I was going to say that even things that we inject, Juvederm, Radiesse, Sculptra, there's an exact sticker that's in the chart, but we know even the exact batch number, where it was made, when it was made, and there is a small possibility that maybe the side effects are clustered to one batch for some reason and all of that information must be in everybody's surgical record. And since every patient can ask for their own surgical record, it just seems like -- like especially the patients with difficulties should be able to find the doctor, I mean, we're talking about 18 years ago, but those medical records must exist. I mean, if we're talking about everything that's happened since 2006 and later when the newer implants came.

And then for patient factors, I think, again, that we should have the possible predisposing conditions of the patients. I mean, we don't know everybody's HLA type, but certainly, most patients know if there are certain family histories and self-histories of

connective tissue disease and self-history of lots of allergies.

DR. LEWIS: All right. The (b) question is whether the benefit-risk profile for textured and smooth implants are different. It seems to me that it's really an extension of whether there's a difference among textured implants; smooth should simply be added as one of those choices. Particularly is there a difference between a smooth implant and a textured implant with the lowest incidence of ALCL, because the data that was presented to us showed a small difference there, but I don't think we know that with any confidence. So, I would say that that needs to be added to the evaluation of the differences in textured implants.

So I guess, Dr. Ashar, what we've come to is that we need whatever is required to get additional data regarding the real differences in textured implants and to include that with sufficient scientific validity to influence your actions in terms of what to do, and since there is compelling reasons to have textured implants available for technical purposes in plastic surgery in certain patients, we need to know what the differences are between the textured implant with the lowest incidence of ALCL and the smooth implant to evaluate whether that method versus using mesh is preferable in terms of fixation.

DR. ASHAR: Okay, thank you.

DR. LEWIS: Are there -- yes, Dr. McGrath.

DR. McGRATH: Just one thing I would add to that, as plastic surgeons are walking away more and more from the use, you heard Sientra mention that they were having trouble getting enough numbers on their textured implants because people are going back -- are using their smooth implants.

I think that if that turns out to be the case and the numbers are low, then we're going to have to use what we're hearing from the studies in other countries and particularly the good ones from Australia where there was a huge gulf of difference between the highly

textured surface and the minimally textured surface, and we'll just have to accept that rather than being able to prove it and have to act at some point based on that information.

So, I think we sort of should think about having a -- I don't know, some sort of a stop-point and not endlessly think about this but go ahead and really decide that if we don't have enough numbers to look at, we ought to use the data that's coming in from other places that is already pretty robust.

DR. LEWIS: I think secondary points that have been raised by several people are that you should look to encourage studies of patient characteristics that influence the interaction with different textured surfaces that affect the outcome and biologic studies of the biofilm and bacterial contamination in regard to the texturing as a causative factor since that seems pretty open at the present time.

DR. ASHAR: Thank you.

DR. LEWIS: Dr. White.

DR. WHITE: I'm a little confused about whether or not surgical technique is important in making or affecting the incidence, and some data was suggested that there was -- there are very specific techniques that can lead to decreased incidence, but then that was sort of rebutted by another presenter. So, I think maybe more data is needed on -- I don't know what specific features would be important to capture it in some kind of database, but some aspects of the surgical technique, I think, should be included.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: So, we're going under the assumption that bacterial contamination and resulting biofilms contribute to BIA-ALCL. If that's the case, then there are techniques that can be employed that many surgeons try to employ all the time to minimize bacterial contamination when you place a prosthetic breast implant in a patient. I don't recall the two conflicting presentations. I know there was -- there were several times they were

mentioning these 14-step plans, so to speak, or 14 steps you can take to minimize bacterial contamination.

DR. LEWIS: Yeah, I might have misunderstood, but I thought the -- Dr. Clemens, I thought --

DR. McGRATH: The remark was there hasn't been a randomized clinical trial about the 14 steps. They've been observationally --

DR. LEWIS: Oh, yeah.

DR. McGRATH: -- regarded. Yes.

(Off microphone comments.)

DR. WHITE: I thought that Dr. Clemens had presented some data that -- to suggest that even when those steps were followed that there were still cases of -- you know, higher than expected cases of ALCL. I may have mis-remembered that.

DR. LEWIS: Dr. Ashar, do you need any further discussion of this question?

DR. ASHAR: Yeah. So, you've -- have you addressed (c)? Is that --

DR. LEWIS: Say again?

DR. ASHAR: Have you addressed Item (c) or have you just gone through (a) and (b) at this point? Because I think Item (c), it would be helpful to have some feedback on that.

DR. LEWIS: Okay.

DR. LEITCH: Yes, they should supply that data. I don't know why we don't have the denominator. That's -- I mean, we should have that data.

DR. ASHAR: I think some of this information is confidential commercial information. Oftentimes some of this information is provided in a different format across different manufacturers, so if you had any specifics on how this information should be provided, it may be helpful.

DR. LEITCH: It's just a number. I don't think it's rocket science. It's just a number.

This is how many --

(Applause.)

DR. LEITCH: This is how many went out there.

DR. LI: The companies are saying they provide the numbers, so --

DR. LEWIS: Could we have a spokesman for the companies come to the podium and address that issue?

MS. DAURIA: Raina Dauria, Mentor.

Mentor does provide in annual reports numbers for implants sold and implants implanted. We do subtract the number of devices that are returned to us because they're not implanted.

MS. KUHNE: JoAnn Kuhne, Sientra.

We submit the same information in our annual reports, but we rely on our device tracking information because it's a more conservative number, and it's more reliable because you know how many -- with the forms back, you know it's already been implanted.

MS. CARTY: Kelly Carty, Allergan.

We supply the same information in our annual reports.

DR. LEWIS: So, the Panel, it sounds like, supports obtaining that information and the companies say they're already doing it.

DR. ASHAR: Thank you. I think that the fact that there is attention on this matter is helpful for us.

DR. LEWIS: Thank you.

Sensing that we have not much more to say about this subject and we still have 20 minutes, we will move on to Question 4 and begin addressing that. We probably won't have time to complete this today, and if not, then we will carry it over to the first deliberations tomorrow, but we will continue until 6:00 p.m. The question here is the Panel

will be asked to discuss methods for assessing and addressing breast implant illness symptoms. And the first discussion is Dr. Benjamin Anderson; the second, Dr. Elaine Jaffe; and the third, Dr. Natalie Portis.

Dr. Anderson.

DR. ANDERSON: So, the question that we're asked to address is parallel to what we were just talking about but now talking about BII. And I think we've been addressing the great challenge of BII because it is this constellation of extremely difficult symptoms that people experience, more commonly women than men, and this falls outside of the implant world. And so, I forwarded a slide. One of the questions is, how are we going to begin by categorizing these symptoms, and if we're from the implant world and the surgical world, we might be missing the boat in terms of how one surveys for these challenging issues. So, I pulled an article from -- you still don't have it?

DR. ASHAR: No, I have it, and it's being forwarded.

DR. ANDERSON: Great.

UNIDENTIFIED SPEAKER: It's being sent over right now.

DR. ANDERSON: So, this comes from a *JAMA* article from 2014 and is a -- not what we have up here yet, but it is a survey tool that is self-administered or can be administered by a clinician on assessing symptoms, their severity, and their frequency, that can be self-reported or done in a clinical setting. And I wanted to put it up not because I'm confident that this is the answer, I am not a rheumatologist, but to say that I think we need to be thinking more along the lines about how we ask the question, what are your symptoms and what do they relate to, because one of the points that we heard was that for a great number of these women it seems to be reported more than 50% were improved by removal of the implants, which means there's another 40% that are not improved by this. It might actually be a related syndrome that we've not yet identified.

So, I think that identifying -- so this -- again, I just pulled this off off-line, but this type of tool could be very helpful in assessing individual patients to start to figure out who's at risk once this has developed. And whether this would be administered before and after implant placement or exactly how it would be done, that I don't know, but I do think that the tool or some tool like this is something that we have to think about and talking to the rheumatology community, I think, is really important for that.

In terms of characterizing the implants, it seems to me the questions are the same for whether you're talking about a malignancy that results from this or this much more common BII problem. Although if I'm understanding correctly, the breast implant syndrome that people are developing is not specific to the textured implants but actually occurs with all of them, and so it's important for people to understand that we're not just talking about the textured as soon as we move into this much more common realm.

I did want to add, parenthetically, that in our hospital we don't use -- the plastic surgeons that I work with do not use the textured implants, but they do exactly what you said, which is that they wrap these smooth implants in AlloDerm, which is a very expensive material, on the order of $20,000 per breast. And so, we need to understand, when we talk about impact of changing things such as doing that, not only is there a medical impact, there's a financial impact, and I do know that insurance companies don't pay for this material.

So, I think developing a set of questions that really gets around BII, studying it better is really important for us, moving forward. Whether we understand the basic science ramifications or not, I think, is really important, and I certainly hear the energy of the people that are so passionate about this, but actually, I think we have to get to how often is it that the implant is causing these terrible symptoms versus how often is it that this is something that people are experiencing because everyone here who's a clinician has lived

with our patients that suffer from these problems who do not necessarily have implants.

DR. LEWIS: Dr. Jaffe.

DR. JAFFE: So, I thought there were also some -- well, issues related to both risk factors, assessing that in greater depth, looking for history or risk factors for autoimmune disease and that those data, I think there's a high priority in collecting those data going forward.

In terms of the implant itself, what I heard was, at least from some of the speakers, that the BII seemed to be more directly related to silicone and perhaps leaking of silicone, rupture of silicone, rather than textured or smooth and that silicone itself was the risk factor. And so, I think we need to collect data on that point.

I also heard that the timing might be critical, and Dr. Zuckerman, in comparing her study and her data to the Institute of Medicine report from some years ago, said that the flaw in the Institute of Medicine report was that they were looking at patients very early on in the course, immediately after the implant, in which the implant might not be playing a role, and so their data was more looking at the long-term effects. But we did hear some patients and some public comment on the fact that the symptoms began almost immediately. So, I think it's critical to look at the timelines in terms of when these symptoms are developing and try and separate out symptoms that are directly related to the implant versus those that might be related to underlying disease and risk factors. And I don't know if Dr. Zuckerman is here, if she can comment on how critical they see the timeline in their data and whether they think that this is a problem that really does take years to develop or whether we should also look at early events.

DR. LEWIS: Dr. Zuckerman.

DR. ZUCKERMAN: Thanks. Oops, is this on? Yeah. Thanks for asking that question. Yes, most of the women that we saw did have a delay, and certainly the studies that you

will get, including some of the studies such as the study in Israel, that a lot of the women who are sick and who have these symptoms have had implants for a longer period of time. But, yes, both in terms of what the women have said today and what we have found in the research, some women get sick right away and some women don't, and it does seem that more women get sick later, but a small proportion do get sick right away, and you know, that's what it seems to look like when we've seen it.

And I also just wanted to clarify that about half the women were silicone, and about half the women were saline, and there was no difference in our group of women who were very sick and wanted their implants out.

DR. LEWIS: Dr. Zuckerman, just to follow up on that point. The one question that hasn't really been highlighted before is what silicone potentially could excite this, and saline implants have a silicone cover, which is essentially identical to a silicone gel cover. On the other hand, a saline implant does not leak silicone, and so if what you just said is correct, that the incidents you're seeing equally between saline and silicone implants, then that would imply any role of the silicone is in the shell and not in the leakage.

DR. ZUCKERMAN: Yeah, to clarify that, from talking to folks who work for the manufacturers, it's my understanding that this silicone outer shell for saline implants is actually different than the silicone outer shell for silicone gel implants. You know, it's all a matter of doing their best to keep the gel inside and so it's -- you know, it's a different formula and so -- and in fact, with the so-called newer gummy bear implants, it's an even different shell. From talking to patients it seems that there is a difference, and sometimes it seems that some of the gummy bear implants have a more immediate negative impact on some women, and also the saline implants, in our experience, seem to have a more immediate negative impact on some women, whereas the silicone gel ones, the problems seem to develop a little bit later but there's no good data on that. I'm just saying what it

seems like from the data that we have, which is limited.

DR. LEWIS: Thank you.

Dr. Portis.

DR. PORTIS: Well, some of what I'll say is somewhat repetitive, but it seems like as we get into this, we see again that we have a surprisingly limited amount of clear and consistent data given the number of years and the number of women involved. And with regard to this question and others, the responsiveness from industry has really been quite inadequate, and we don't have the long-term data we need from industry despite it being required in post-approval studies. So, one of the things I think we need is for FDA to continue to strongly enforce the compliance issues.

I'm jumping around a little bit. You know, when we start talking about these new shells and all these different combinations, it comes back to this question of, you know, we need to have, as a baseline, a full list of ingredients and that it's required --

(Applause.)

DR. PORTIS: And that it be given to patients because now we've got a whole soup of things inside of women and we don't know what they're reacting to.

(Applause.)

DR. PORTIS: You know, I feel like we failed women with regards to implants; we failed to inform, we failed to follow up, we failed to listen, and perhaps we've even failed physicians in giving them the tools to do all of this adequately. So, we need to listen to patients, and we need, as we're talking about it, to have an organized and uniform way to do this. And I think then we come back to this issue of what is consistent and full-informed consent, what does that really look like? I like the idea of a brief simple checklist that's done by physicians themselves that is very clear. Most patients don't ever see any package inserts, so the onus really is on the physicians to fully inform and not just reassure patients.

You know, someone brought up that, yes, this is frightening, we don't want to frighten patients, but I trust women to be able to handle this information if they're really given it.

So, I think if we have more complete informed consent, then we can go to the next step, that patients know what to look for and they may be more likely to follow through when they start to get symptoms. And then it goes to that next step of we need a simpler way of detecting and using ultrasound because it sounds like the MRIs are not just working; it's onerous in a number of ways.

And then the issue that we've talked about that we really need baseline information from every patient because we don't know, does the implant set off some of these symptoms due to preexisting conditions? Some of the presenters brought up that there might blood tests that we can look at and immunochemistry of patients to see if they have predisposing factors. And we need consistent practices to look at family history and health status and quality of life at baseline because, again, then we're looking at this later, we don't know where patients started. And I think all doctors need to have this. As we mentioned, this isn't just done by plastic surgeons; patients present with these symptoms to a number of doctors, and maybe, like we've started to do with like postpartum depression, if we have a routine way that doctors can, when they know a patient has an implant, ask a series of questions. And I guess there's lots more I could say but -- and the other thing, people bring up about the black box warning, which I think would be good, but again, I think it's inadequate. I don't think that -- you know, we have patients here who are informed and engaged, but I don't think the average patient knows what a black box warning means and knows to look for it or even where to look for it.

DR. LEWIS: Thank you.

(Applause.)

DR. LEWIS: It's 5 minutes to 6:00 and launching into discussion of the individual

points here, I think, would not allow us sufficient time to deal with those, so I'm going to call the adjourned meeting today, and we'll continue with the discussion of this topic tomorrow and devote the first 30 minutes of the session before lunch to the additional discussion of this, and we'll try to take these individual (a), (b), (c) points at that time. So, at this point, we stand adjourned until 8 o'clock tomorrow morning.

(Whereupon, at 5:55 p.m., the meeting was continued, to resume the next day, Tuesday, March 26, 2019, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

March 25, 2019

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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